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British Journal of Anaesthesia

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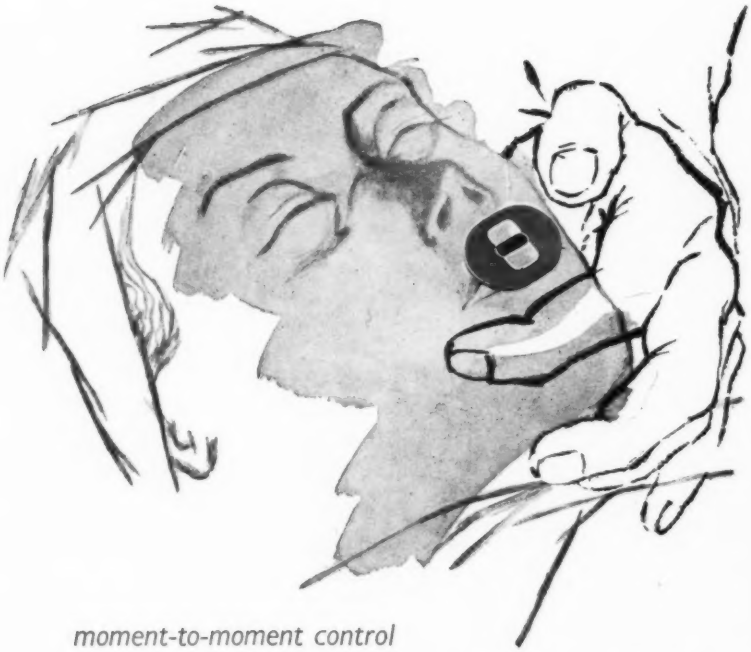

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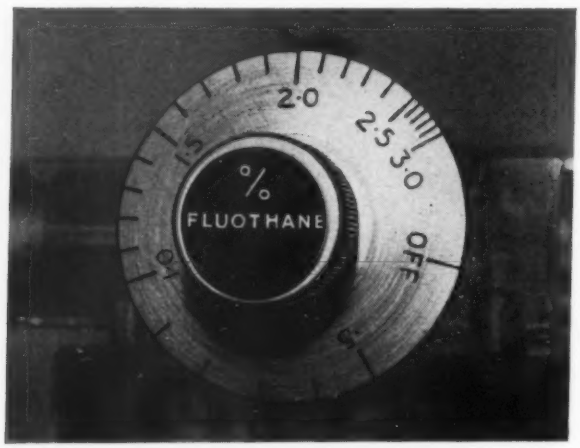

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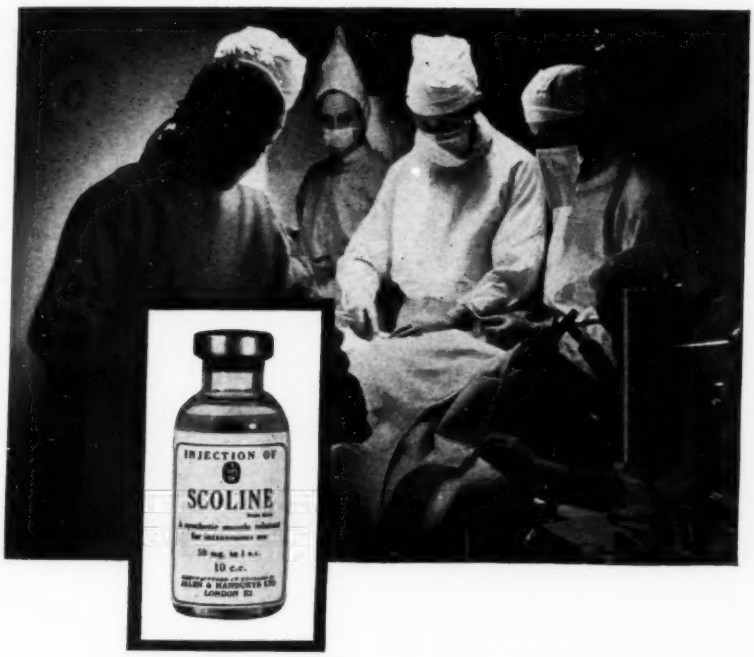

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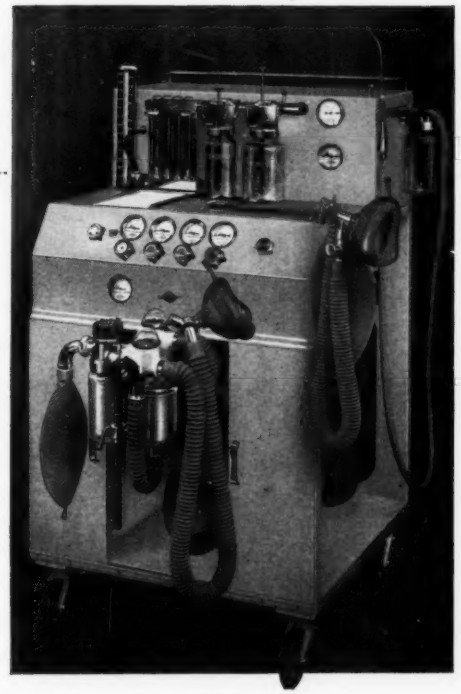

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXIX No. 8 AUGUST 1957

EDITORIAL

CLINICAL HYPOXIA

Dr. Paluel J. Flagg, president of the National Resuscitation Society Inc. of America, recently visited Europe and presented the Deans of the University Colleges of Trinity, London, Paris, Heidelberg, Rome, Barcelona, Madrid and Lisbon with a document for their consideration. Following a perusal of Dr. Pinkerton's Editorial in our May number he thought that our readers would be interested in it and has sent us a copy. The document deals with the subject of "Hypoxia". That the matter is one of extreme urgency is evidenced by the fact that there are at least 50,000 deaths annually in the U.S.A. due to it. Dr. Flagg emphasizes the fact that clinical hypoxia is by no means limited to the operating theatre and the hospital ward, but cuts across the entire field of medicine. It ranges from earliest days, as asphyxia neonatorum, to the last episode cerebral haemorrhage, from mountainous heights to submarine depths, from solid bodies that obstruct the airways to gases that suffocate, from the paralysis of polio to the spasms of tetanus, and from accidents of all kinds from automobiles to avalanches. Not only is the matter urgent from a national standpoint, but each case is an emergency and needs immediate skilled treatment. It is just here that Dr. Flagg thinks much might be done to reduce this yearly mortality. An occasional reference to hypoxia throughout the student years is not enough. Moreover, he thinks the medical profession as a whole is less able to deal with the situation than formerly and that largely by reason of the fact that the student today, the house surgeon, unless training to be an anaesthetist, avoids all opportunities of giving anaesthetics and consequently is unfamiliar with the unconscious patient.

This has come about of late years because anaesthesia has extended its borders and demands the whole time and thought of the present day anaesthetist. There is no time or opportunity for the occasional giver of anaesthetics and so he misses valuable experience which leaves him at a loss when confronted with the urgency of the unconscious patient.

What is the remedy? Dr. Flagg suggests nothing less than an intensive course on the subject, under the heading of "Interdepartmental Correlation". The resources of the University and the Hospital in academic and clinical instruction are brought to bear on the student, the resident and the practitioner. What part has the anaesthetist to play in all this? It might be said that he is the keystone of the arch. The popular anaesthetic technique of the last decade has involved the use of relaxants and other powerful drugs. The depression of function desired, muscular tone for example, has been found to be associated with depression of other functions inconvenient and even dangerous; thus we find respiratory paralysis requiring artificial respiration accompanying relaxation and often associated with hypercarbia and alteration in the pH of the body fluids. The result is that the anaesthetist has become an expert in intravenous injection and artificial respiration and has acquired with the physicist understanding of the partial pressures of gases, and with the biochemist familiarity with the transference of ions. He reads the signs of approaching heart failure by means of the electrocardiogram; unexpected collapse from haemorrhage or convulsions are emergencies with which he is acquainted. Thus "circled through

[*Continued on page 362*

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THE USE OF A HOMATROPINIUM DERIVATIVE TO PRODUCE CONTROLLED HYPOTENSION

BY

J. D. ROBERTSON AND JOHN GILLIES

Department of Anaesthetics, Royal Infirmary, Edinburgh

AND K. E. V. SPENCER

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THE PHARMACOLOGY OF PHENACYL HOMATROPINIUM CHLORIDE (TROPHENIUM*)

IN the course of an investigation of hypotensive drugs, a series of tropinium esters was prepared and examined pharmacologically (Johnston and Spencer, 1956). One of the esters, phenacyl homatropinium chloride (Trophenium) (fig. 1), was found to be a powerful ganglion blocking drug having a short duration of action. This suggested that it might be used to produce controlled hypotension in anaesthesia. The following is a summary of its main pharmacological actions.

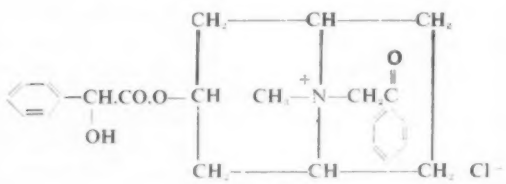

FIG. 1

Formula of Trophenium.

Ganglion Blocking Actions.

Using the cat nictitating membrane preparation, Trophenium was found to be ten times as potent as hexamethonium iodide (C6) as a ganglion blocking agent. Its duration of action measured at the ED50 was half that of hexamethonium. Trophenium was found to be one and a half times as potent as trimetaphan (+) camphorsulphonate (Arfonad, Roche), with a similar duration of action at the ED50.

Actions on the Circulation.

The intravenous injection into the anaesthetized cat of a small dose (0.1 mg/kg) of Trophenium caused a short-duration fall in blood pressure of about 70 mm Hg. When the blood pressure had reached its lowest level an injection of a large dose of hexamethonium produced no further fall. Similarly, the injection of a large dose of Trophenium during the maximal hypotension produced by hexamethonium caused no further fall in blood pressure. Trophenium abolished the pressor response to injections of small doses of nicotine. It is likely, therefore, that the hypotensive action of Trophenium is due to blockade of the sympathetic ganglia. In the cat, Trophenium, by intravenous injection, was found to be twenty times as potent as hexamethonium as a hypotensive agent. Its duration of action was half that of hexamethonium at the ED50.

Figure 2 illustrates a typical experiment in which the depressor actions of Trophenium and trimetaphan were compared in a cat anaesthetized by chloralose-urethane. The drugs were injected in random order. The upper graph shows the duration of action of the drugs as measured by the time taken from the injection until the blood pressure had returned half way back to the pre-injection level. The duration of action of trimetaphan was much greater than that of Trophenium as the dose exceeded 0.1 mg/kg.

The lower graph shows that the maximal fall in blood pressure produced by trimetaphan was greater than that produced by Trophenium or by a large dose of hexamethonium. This can be taken as additional evidence that the depressor actions

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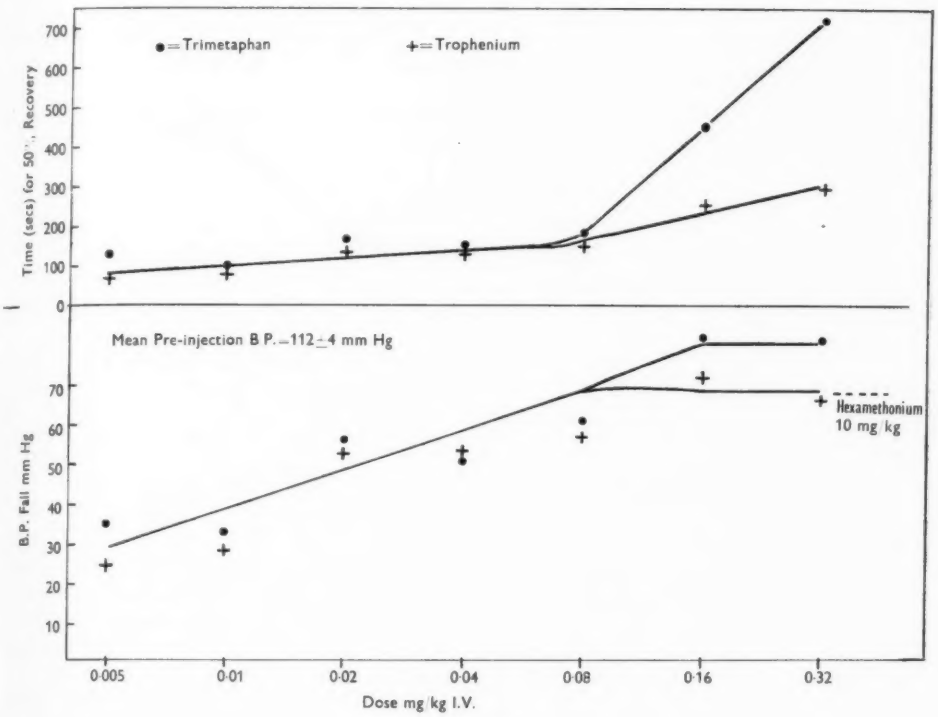

FIG. 2

Comparison of the hypotensive actions of Trophenium and trimetaphan. Drugs given by intravenous injections of saline solutions in the cat anaesthetized by chloralose-urethane. Upper graph shows the duration of action of the drugs and the lower graph their effect on the blood pressure.

of trimetaphan are not entirely due to its ganglion blocking action (McCubbin and Page, 1952).

Using cats anaesthetized by pentobarbitone sodium, controlled hypotension was produced by injections, repeated every 30 seconds, of 0.02 mg/kg of Trophenium. It was found that controlled hypotension could be produced more conveniently by means of an intravenous infusion of the drug using dosage rates of from 0.2 to 0.1 mg/kg/min. Figure 3 illustrates a typical blood pressure tracing made during an infusion of Trophenium. It shows that a few minutes after the blood pressure had fallen following the start of the infusion, there was a slight compensatory rise in pressure to a steady level. Recovery was rapid after stopping the infusion. This compensatory rise in pressure was often, though not invariably, seen and it was also found to occur with comparable infusions of trimetaphan. Single injections of Trophenium and of hexamethonium iodide failed to lower the blood pressure again during the compensatory rise and it is likely that this response represents a spontaneous partial return of the tone of the blood vessels and is similar to that seen in sympathectomized patients. Zaimis (1955) showed that this could be explained by the peripheral vessels becoming more sensitive to the actions of adrenaline and noradrenaline during ganglion blockade.

Table I shows the effect of varying the infusion rate of Trophenium on the recovery time as measured by the interval from the end of the

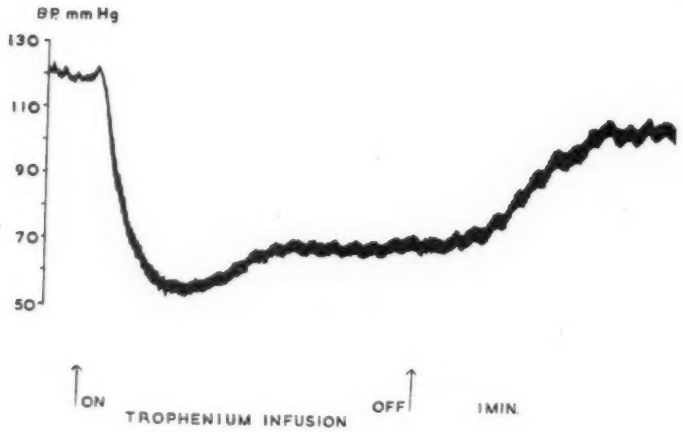

FIG. 3

Controlled hypotension produced by the intravenous infusion of 0.1 mg/kg/min of Trophenium in the cat anaesthetized by pentobarbitone sodium.

TABLE I

The effect of varying the infusion rate of Trophenium on the B.P. recovery time in the cat

Infusion rate of Trophenium	Total dose	B.P. recovery time (mean)
mg/kg/min	mg/kg	sec
0.1	2.0	90
0.2	2.0	208
0.4	2.0	330
0.8	2.0	453
1.6	2.0	497

infusion until the blood pressure had returned half way back to the pre-infusion level (50 per cent recovery time).

Very prolonged recovery times have not been seen following infusions of Trophenium. However, they have occasionally been seen with infusions of trimetaphan in the anaesthetized cat. In one experiment the 50 per cent recovery time following an infusion of 2 mg/kg trimetaphan at a dosage rate of 0.1 mg/kg/min was 185 minutes. The blood pressure did not return to its original level until 375 minutes after the end of the infusion.

The pressor drugs, adrenaline and methylamphetamine, are very effective antagonists to the hypotension produced by Trophenium (figs. 4 and 5). Since Trophenium blocks the reflex vasodilator responses to pressor drugs, their effects are potentiated during Trophenium blockade. Therefore care would have to be taken to use smaller doses than usual of these drugs if they are required during infusions of Trophenium.

Trophenium was not observed to produce any adverse cardiac effects in anaesthetized cats or in conscious or anaesthetized rabbits. Heart block was not seen and even with lethal doses no changes, apart from bradycardia, occurred until anoxia was marked.

Actions on the Respiration.

When administered to anaesthetized cats at dosage rates of up to 3.2 mg/kg/min, Trophenium produced a slight stimulation of respiration. Table II illustrates the results which were obtained. The respiratory rates and minute volumes are presented as percentages of the pre-infusion values.

Acute Toxicity.

Table III shows the toxicity of Trophenium to mice by various routes.

After administration of Trophenium by the subcutaneous and intraperitoneal routes, the first symptom to be seen was that of sedation which was followed by paralysis and then respiratory

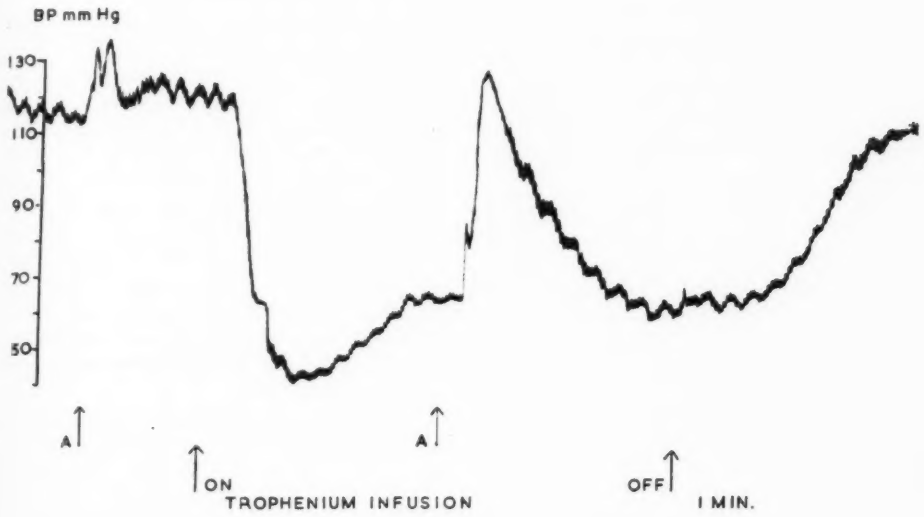

FIG. 4
Antagonism to Trophenium hypotension in the cat anaesthetized by pentobarbitone sodium. Trophenium dosage rate 0.1 mg/kg/min. At A, adrenaline hydrochloride 3 μg.

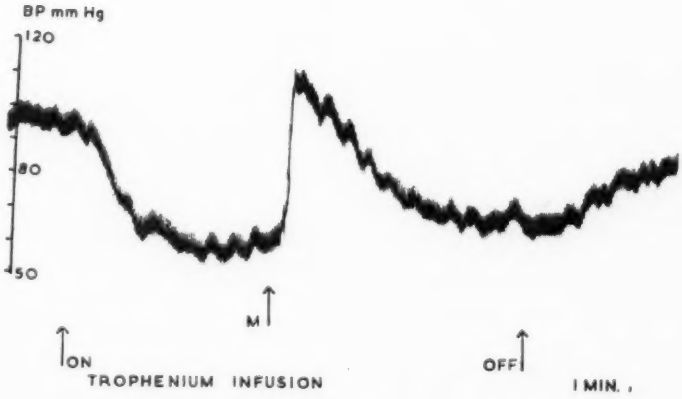

FIG. 5
Antagonism to Trophenium hypotension in the cat anaesthetized by chloralose-urethane. Trophenium dosage rate 0.1 mg/kg/min. At M, methylamphetamine 0.1 mg.

TABLE II
The effect of varying the infusion rate of Trophenium on the respiration in the cat

Infusion rate of Trophenium	Total dose	Respiration rate	Minute volume
mg/kg/min	mg/kg	per min	ml/min
Control	—	100	100
0.1	2.0	101	108
0.2	2.0	114	147
0.4	2.0	117	144
0.8	2.0	104	118
1.6	2.0	107	116
3.2	2.0	101	106

TABLE III
The acute toxicity of Trophenium in mice

Route	Concentration of Trophenium	LD50
	mg/ml	mg/kg
Subcutaneous	18	426
Intraperitoneal	10	180
Intravenous	0.5	16
(I.V. dosage rate 120 mg/kg/min)		

failure. Examination of the dead animals showed no tissue damage at the injection sites, and all the organs appeared to be normal. Paralysis occurred immediately after intravenous injections, but in the animals which survived recovery was rapid, being complete within one minute after the injection.

Pilot studies showed that Trophenium had similar toxicities in rats, rabbits and cats.

Subacute Toxicity Studies.

Newly weaned Hooded Wistar rats received daily subcutaneous injections of 50 mg/kg of Trophenium (5 per cent w/v in 0.9 per cent saline). No significant difference was observed between the growth rates of the control group, the group injected with saline, and the group injected with Trophenium over the period from weaning until maturity. The Trophenium injections caused local tissue damage with dry scab formation. This cleared within 2–3 days of changing the injection site.

The Production of Tissue Damage by Trophenium.

Although Trophenium caused tissue damage by subcutaneous injection in rats, it was not found to do so in the mouse, rabbit, cat, monkey and man.

The Side Effects of Trophenium.

The atropine-like side actions of the drug are negligible. The subcutaneous injection of a 5 mg dose in man did not produce tachycardia, dryness of the mouth or skin and vision was not affected. Animal experiments indicate that atropine is more than one thousand times as active as Trophenium in those respects; for example, the topical application of a 50 mg/ml solution of Trophenium to the eyes of mice failed to produce mydriasis, whereas the pupils were fully dilated by a similar application of atropine sulphate solution containing 10 μg/ml. Similar results for the relative potency of the two drugs were obtained using them as antagonists to the action of acetylcholine on the isolated guineapig ileum.

Trophenium was not found to be a potent histamine liberator. The histamine-liberating properties of Trophenium and trimetaphan were examined by comparing the weal responses to intradermal injections of the drugs in the human forearm. Figure 6 illustrates some results obtained and shows that Trophenium is very much less active than trimetaphan as a histamine liberator. Using the chloralose anaesthetized cat in which the ganglia had been blocked by a large dose of hexamethonium, an intravenous injection of 1 mg/kg of Trophenium caused no further fall in the blood pressure whereas 30 seconds after the intravenous injection of 0.1 mg/kg of trimetaphan there was a fall in blood pressure of 31 mm Hg indicating a release of histamine by the drug (Macintosh and Paton, 1949).

Conclusions

The animal experiments indicate that Trophenium is a safe and reliable drug which can be used to produce controlled hypotension in anaesthesia.

Its hypotensive action appears to be solely due to blockade of the sympathetic ganglia. The blood pressure rapidly returns to normal following the end of an infusion and no very prolonged recovery times have been seen, although they have sometimes occurred following comparable experiments with trimetaphan. The hypotensive effect of Trophenium is readily reversed by adrenaline and methylamphetamine.

Even in lethal doses, Trophenium had no adverse effects on the heart.

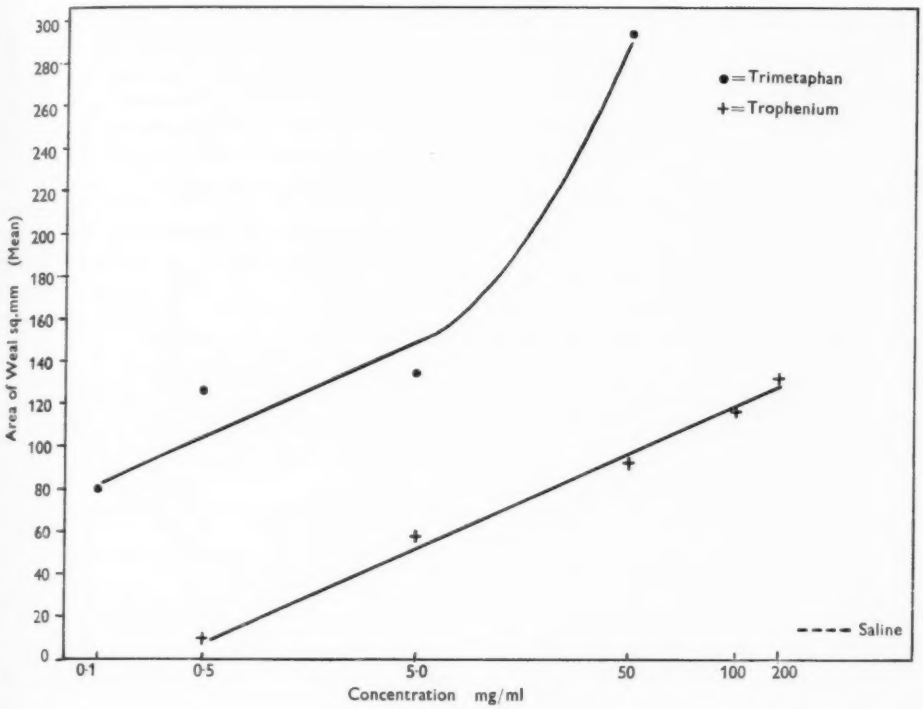

FIG. 6

Comparison of the histamine liberating properties of Trophenium and trimetaphan using the weal response. Drugs injected in saline solution intradermally in the human forearm using an injection volume of 0.02 ml.

Trophenium was found to be much less active than trimetaphan as a histamine liberator. It has negligible atropine-like side actions.

It is suggested that Trophenium could be administered as an intravenous saline drip in order to produce controlled hypotension during anaesthesia. Suitable concentrations of the drug would be from 0.5 mg/ml to 2 mg/ml and in these concentrations Trophenium is compatible with thiopentone.

THE USE OF PHENACYL HOMATROPINIUM CHLORIDE (TROPHENIUM) TO PRODUCE CONTROLLED HYPOTENSION DURING SURGICAL OPERATIONS

In 1953 Nicholson, Sarnoff and Crehan described the use of the new ganglion blocking agent trimetaphan camphorsulphonate (Arfonad) for the production of rapidly reversible hypotension during 25 surgical operations following its use by Sarnoff, Goodale and Sarnoff (1952) to produce graded reduction of arterial blood pressure in man in the treatment of acute pulmonary oedema. The first report in Britain of the use of trimetaphan to produce controlled hypotension during anaesthesia and surgery was by Magill, Scurr and Wyman (1953) who described their findings in five patients. Since that time many reports concerning its use in this country, on the Continent and in America have appeared in the literature.

We have had considerable experience with trimetaphan during the past 3½ years and have for the most part found it a reliable hypotensive agent. The following disadvantages have been reported:

(1) Although trimetaphan acts as a ganglion

blocking agent (Randall, Peterson and Lehmann, 1949) it is also said to owe part of its action as a hypotensive agent to a direct effect on the vessels (McCubbin and Page, 1952) and to the release of histamine (Mitchell, Newman, MacGillivray and Clark, 1951; Payne, 1956). Theoretically, at least, it would seem that a drug causing such a complex effect would be less reliable than one which acted only at one point.

(2) Scurr and Wyman (1954) have described the development of tachyphylaxis in two cases following the administration of trimetaphan so that some patients become resistant to its hypotensive action.

(3) Occasionally the degree of hypotension has been marked and has remained so for a considerable period after the administration has been discontinued. In the presence of profound systemic arterial hypotension the glomerular filtration rate is reduced and, as trimetaphan is excreted partly by the kidneys (Gertner, Little and Bonnycastle, 1955), might lead to a continuance of hypotension. This would be particularly liable to occur in patients with renal disease (Little, 1956).

(4) Tachycardia due to autonomic imbalance may sometimes develop (Little, 1956).

For these reasons we felt that a drug having a duration of action comparable to that of trimetaphan, but which had a pure ganglion blocking action and gave no evidence of histamine release, was worthy of clinical trial. Such a drug is phenacyl homatropinium chloride (Trophenium —Duncan, Flockhart & Co. Ltd.).

Selection of Patients.

The criteria used in selecting the patients for this trial were based primarily on the indication for controlled hypotension in surgery which one of us has stated to be " that situation in which the advantages will be of certain benefit to the patient and likely to outweigh the assumed risks." More specifically, the general state of the patient, type of operation and the skill and experience of the anaesthetist and operator must be assessed in each individual case before the use of controlled hypotension can be decided upon or justified. The chief contra-indications are advanced degenerative cardiovascular disease, renal and hepatic disease and low blood volume.

Operations.

The operative procedures in which hypotension was induced with Trophenium may be divided into two groups—general and thoracic (table IV). There were 29 males and 10 females in the general surgical group and 21 males and 15 females in the thoracic group. In the latter, one patient was subjected to two separate operations, hypotension with Trophenium being used on both occasions.

TABLE IV

General surgery	
Gastro-intestinal operations	6
Urological operations	8
Orthopaedic operations	8
Hernial repairs	11
Others	6
Thoracic surgery	
Thoracoplasties	4
Segmental resections	20
Lobectomies	5
Lobar and segmental resections	4
Pneumonectomies	3
Decortication	1

Age.

In the general surgical group the average age was 50 years (S.D. 17.6), a considerably higher figure than in the thoracic group where the average was 38 years (S.D. 12.5) (table V).

TABLE V

Age	General surgery	Thoracic surgery
10–19	1	2
20–29	6	8
30–39	5	14
40–49	6	8 (1 twice)
50–59	11	4
60–69	5	1
70–79	3	–
80–89	2	–
Total	39	37 operations on 36 patients
Average	50 (S.D. 17.6)	38 (S.D. 12.5)

Pre-operative State.

The two groups were hardly comparable because, although the patients undergoing thoracic operations were younger than those in the general surgical group, their general condition was poor,

all of them having extensive pulmonary tuberculosis which in 22 of the 36 cases was bilateral. On the other hand, apart from two cases in this group with diabetes mellitus, which was well controlled under effective medical supervision, there was little else in the way of concurrent disease. In contrast, several of the older patients in the general surgical group were suffering from chronic disease of the respiratory or circulatory system or both, four were extremely overweight and two had pernicious anaemia (table VI).

TABLE VI

Pre-operative state	General	Thoracic	Total
No concurrent disease	22	30	52
Respiratory			
Chronic bronchitis and emphysema	5	–	5
Circulatory			
Systemic hypertension	8	–	8
Previous lumbar sympathectomy	1	–	1
Blood diseases			
Pernicious anaemia	2	–	2
Metabolic diseases			
Obesity	4	–	4
Malnutrition	–	2	2
Diabetes mellitus	–	2	2
Myxoedema	–	1	1
Psychosis			
Paranoia	–	1	1
Total number of conditions	42	36	78
Total number of patients	39	36	75

Anaesthetic.

All patients were, of course, under a general anaesthestic. This varied considerably between the two series but within each series a standard technique was employed. Where necessary to obtain adequate muscular relaxation or to allow the respiration to be controlled the general anaesthetic was supplemented by a muscle relaxant agent. The methods employed can be summarized as follows:

Thoracic surgical cases. Induction of anaesthesia with thiopentone sodium 150–500 mg (average 480 mg) and maintenance with cyclopropane and oxygen. In one case nitrous oxide and oxygen were used for induction. As the patients were on controlled respiration during the period when the pleural cavity was open they all received d-tubocurarine chloride, the dose varying from 20 mg to 52.5 mg, the average being 34.2 mg. In one case 160 mg gallamine triethiodide was used instead of d-tubocurarine chloride. Ventilation was achieved by manual compression of the bag of the Waters to-and-fro absorber unit.

General surgical cases. On 37 of the 39 occasions anaesthesia was induced by intravenous thiopentone sodium. The dosage varied from 200 mg to 700 mg, the average being 490 mg. A light plane of surgical anaesthesia was then maintained with a nitrous oxide-oxygen-trichloroethylene mixture from a Boyle's apparatus, except in four cases in which Fluothane-oxygen was used. In two of these Fluothane-oxygen was also given to induce anaesthesia. Thirty of the cases received at least one intravenous injection of gallamine triethiode, the total amount of this relaxant varying from 60 mg to 160 mg with a mean of 100 mg. In seven cases d-tubocurarine chloride was employed, the dosage varying from 15 mg to 40 mg with a mean of 25 mg. In two of the patients receiving Fluothane and oxygen no relaxant was given. In four patients undergoing abdominal operations a mechanical positive pressure respirator ("Pneumomatic") was employed to ensure adequate pulmonary ventilation. During extra-abdominal operations the patients were allowed to breathe spontaneously.

Hypotensive technique.

The blood pressure was recorded by a mercury sphygmomanometer before and after induction of anaesthesia. In all cases in the two series, once a steady level of light surgical anaesthesia had been reached, an intravenous infusion containing Trophenium was set up by direct puncture of the cephalic vein on the radial side of the wrist, the standard blood-giving set being employed. The patient was then put into position for the operation. Various concentrations of Trophenium in normal saline solution were employed (table VII).

TABLE VII

Concentration of Trophenium (mg/ml)	Number of administrations	
	Thoracic series	General surgical series
0.5	6	7
1.0	18	3
1.5	1	–
2.0	12	25
5.0	–	4

The most satisfactory concentration was found to be 2 mg/ml. The arterial blood pressure was again checked and the intravenous administration begun. Initially the rate was set at about 100–120 drops per minute and while this was being counted by a nurse the blood pressure level was repeatedly checked by the anaesthetist. Once the pressure was falling steadily and had reached a systolic level about 10 mm Hg higher than the final level desired, the drip rate was slowed to approximately 40–60 drops per minute. The level of systolic blood pressure aimed at varied on each occasion and was decided from the nature of the operation, the general condition of the patient—in particular, his resting blood pressure level—and later, once the operation had started, by the amount of bleeding which was actually occurring. Preparation of the patient for operation was now started. A careful check was kept on blood pressure at this time and appropriate adjustment of the drip rate made if the fall became excessive or the pressure began to rise. Preparation of skin and towelling having been completed, a final blood pressure check was made and if this was satisfactory the operation was started. As had been found previously with trimetaphan, it was advisable to make sure that a satisfactory level of hypotension had been achieved before the operation was begun. Once the operation was well under way the stability or otherwise of the blood pressure level and the amount of bleeding in the wound determined the drip rate. The level of blood pressure was checked at frequent intervals throughout the operation. In addition, other observations made included the pulse rate, rhythm and volume, the state of the pupils, the colour and dryness of the patient's skin, the capillary refill time, the respiratory rate and tidal exchange, and the level of anaesthesia. Where possible drifts in the blood pressure level were anticipated, suitable adjustment of drip rate was made to counteract them before they became excessive. In general, however, the ideal was to attain a satisfactory blood pressure level rapidly and thereafter to make as few adjustments to the drip as possible. Excessive or sudden falls in blood pressure below the range desirable for the individual case usually recovered rapidly when the drip was stopped. It was important, however, to keep a close and constant watch on the pressure at such times, both to avoid excessive prolongation of extreme hypotension and to observe when recovery of blood pressure was beginning, because once it had started to rise it frequently did so very sharply, and if the administration of a hypotensive agent was not quickly restarted, the pressure might reach a higher level than desired. Methylamphetamine or methoxamine was always kept readily available to combat excessive hypotension should this develop during or after the operation.

Results

A rapid fall in mean arterial blood pressure occurred in every case in which Trophenium was administered. In two cases in the general surgical and in four cases in the thoracic series, although the systolic blood pressure fell satisfactorily initially, difficulty was encountered in maintaining a satisfactory steady level, frequent alterations in drip rate being accompanied by swinging of the pressure. In all these cases the drug was being given in a low concentration. Much more stable conditions were obtained when it was given in a strength of 2 mg/ml later in the investigation. In three other cases in the general surgical series the

initial fall was not maintained, the blood pressure becoming fixed at an inadequate level of between 80 and 110 mm Hg which was unaffected by changes in drip rate.

Occasionally during the maintenance of hypotension the level of blood pressure became unnecessarily low. On some occasions, in fact, for a short period the sounds were completely inaudible. Sometimes this may have been due to difficulty in hearing the very faint sounds, especially as the pulse pressure frequently narrowed considerably so that the range over which sounds could be heard was limited to only a few beats. Following stoppage of the infusion spontaneous recovery of blood pressure usually occurred. This was sometimes not as rapid as might have been expected from the pharmacological studies, but in every instance the colour remained good and spontaneous respiration, when present, was unaltered. A pressor agent was used in only one of these cases.

Mean systolic blood pressure values at various stages of the operation with standard deviations are shown in table VIII.

Mean values with standard deviations for the duration of operation, anaesthetic and Trophenium administration, recovery time of blood pressure and total dose of the hypotensive agent are shown in table IX.

For the purpose of assessing recovery the arbitrary systolic pressure value of 100 mm Hg was accepted for all cases. Whilst the use of a fixed level such as this is open to objection in view of the individual differences in starting blood pressure level, in general, once the systolic pressure had regained 100 mm Hg the patients were considered fit for return to the ward where they were kept under close nursing supervision with the foot of the bed raised on blocks for 4 to 6 hours. It can be seen that the time taken for the blood pressure to recover when the hypotensive infusion was discontinued differed considerably in the two series and there was a wide variation amongst individual members of each group.

The pulse rate showed no consistent change during controlled hypotension with Trophenium except in the three cases in which the pressure became fixed at an inadequate level. In these cases the pulse rate rose to over 100 beats per minute.

The neuromuscular blocking action of d-tubocurarine chloride and gallamine which were used in the usual dosage was not noticeably potentiated by Trophenium in the dosage employed in this investigation.

Postoperative complications.

In the two series in which controlled hypotension was employed one patient died. This was an

TABLE VIII

	Thoracic cases		General surgical cases	
	Mean systolic B.P. (mm Hg)	S.D.	Mean systolic B.P. (mm Hg)	S.D.
Before induction	134	17.2	139	26.7
At time of incision	71.3	24	68.2	12.7
At time of stopping Trophenium infusion	65.3	14.2	70.8	15.6
At end of operation	98.4	19.4	95.9	25.4
Lowest B.P. during infusion of Trophenium	46.7	9.9	57.3	10.3
Highest B.P. during infusion of Trophenium	85.2	16.2	83	23.2
Average level of B.P. during infusion	67	7	72	13

TABLE IX

	Thoracic series		General surgical series	
	Mean	S.D.	Mean	S.D.
Duration of operation (min)	93.1′	(27.5)	49.4′	(23.4)
Duration of anaesthetic (min)	112.5′	(28.8)	67.4′	(27.8)
Duration of Trophenium infusion (min)	74′	(24.8)	44.2′	(23.4)
Total dose Trophenium (mg)	350	(222)	326	(107)
Recovery time of B.P. (min)	24.2′	(23.4)	15.4′	(10.5)

old man who had a transvesical prostatectomy carried out for benign prostatic hypertrophy. His pre-operative, operative and immediate postoperative states were satisfactory, but his condition gradually deteriorated and he died of bronchopneumonia 26 days after the operation.

Of the non-fatal postoperative complications eight occurred in the general surgical group and seven in the thoracic group (table X).

TABLE X

Postoperative complications	General surgical series	Thoracic series
None	31	30
Death (26 days after operation)	1	–
Haemorrhage	1	3
Respiratory infection	2	–
Lobar collapse	1	–
Respiratory inadequacy	–	2
Wound infection	1	–
Urinary infection	1	–
Urinary retention	–	1
Diarrhoea	–	1
Parotitis	1	–
Total	39	37

In four cases in which hypotension was induced with Trophenium there was bleeding from the operation site in the postoperative period.

One was an elderly man who had a transvesical prostatectomy performed. During the operation the mucous membrane of the bladder was found to be thickened and red, with a velvet appearance, bleeding where it was touched. The prostate was enucleated after considerable difficulty in obtaining a reasonable line of cleavage on the right side. Moderate bleeding from the prostatic bed followed but was controlled by diathermy, the blood lost being replaced as it occurred. A Foley catheter was passed per urethram and the bulb blown up sufficiently to counteract oozing from the prostatic bed. The blood pressure returned rapidly to the pre-operative level when the drip containing the hypotensive agent was stopped, and the patient was returned to the ward. Half an hour later, however, he was brought back to the operating theatre because of clot retention, and re-anaesthetized. No hypotensive drug was given on this occasion. There was found to be a general oozing from the trigonal area of the bladder mucosa and a brisk haemorrhage from the prostatic bed. Several attempts were made to stitch the prostatic bed with a Harris boomerang needle, but on each occasion the stitches cut out. Haemostasis was obtained by means of a gauze pack in the prostatic bed and layers of oxycel gauze pressed into the posterior lip of the prostatic bed and the surrounding area which was practically denuded of mucosa. A total of 7 pints of blood was given to this patient who made a satisfactory recovery, the pack being removed on the 5th day.

In the thoracic series a recorded drainage into the water seal bottle of 30 fl.oz (750 ml) or more within the first 48 hours after operation was the criterion of significant postoperative haemorrhage. In three cases in the series following segmental resection bleeding occurred requiring further transfusion of blood.

None of the cases showed suppression of urinary secretion after operation. One patient, a man aged 25, developed urinary retention in the immediate postoperative period for which he required catheterization on one occasion. There was no case of paralytic ileus and in fact the only patient who developed bowel symptoms showed signs of hypermotility. As these did not develop until the 4th day after operation and consisted of diarrhoea with blood and mucus which gradually improved on stopping chemotherapy, it seems more likely that they were related to the latter than to any autonomic disturbance produced by Trophenium. There were no cases of thrombophlebitis or of cerebral or coronary thrombosis following operations in which controlled hypotension was used in this series.

Discussion

Control of blood pressure. If arterial hypotension is to be induced as an aid to haemostasis in a carefully selected group of patients undergoing surgical operations in which haemorrhage is likely to cause serious interference with the successful conduct of the operation, the emphasis must be on its controllability. Thus, the longer acting methonium compounds and pendiomide frequently prove unsatisfactory for, if the initial dose is too small, subsequent doses are often ineffective in producing a satisfactory further fall of the blood pressure. On the other hand, when a large initial dose is given, the fall in pressure produced may occasionally be excessive and require the use of a pressor agent to avoid dangerous and prolonged depression of blood pressure. Once the pressure has been raised in this way it is often extremely difficult to modify it by the subsequent injection of a hypotensive drug. Thus a drug with a short duration of action given continuously in

the form of a dilute intravenous infusion would appear to offer a greater chance of controllability. Trimetaphan has been found to possess this advantage but to be less satisfactory in certain other respects.

The exact nature of the hypotensive action of trimetaphan is rather ill defined. It is a powerful ganglion blocking agent (Randall et al., 1949) and it also has a direct vasodilator action (McCubbin and Page, 1952). The intravenous injection of trimetaphan in dogs (Randall et al., 1949; Mitchell et al., 1951) and in man (Payne, 1956) is accompanied by a release of histamine which might be responsible in part for the hypotension produced by the drug. As far as can be seen from the pharmacological experiments Trophenium owes its hypotensive action to its ganglion blocking properties; it has no direct dilator action and does not release histamine to any significant extent.

Tolerance. Many authors have reported the development of tolerance with ganglion blocking drugs, both when they are given orally in the treatment of systemic hypertension and when given intravenously to induce hypotension during surgery. In the latter instance this may occur within a few minutes, a condition known as tachyphylaxis. It probably occurs less frequently with trimetaphan than with hexamethonium (Voorhoeve, 1955). Voorhoeve (1955) advocated the use of an initial intravenous injection of 100 mg of undiluted trimetaphan to overcome this difficulty and found that following this a stable level of hypotension could be maintained by the continuous infusion of 1 per cent trimetaphan in 5 per cent glucose solution at a rate varying between 1 drop per 4 seconds to 4 drops per second. We have found, however, that in practically every case with trimetaphan this difficulty in achieving a satisfactory fall in blood pressure can be overcome by the use of a high initial drip rate. In the present series with Trophenium, as has been described, we always maintained a fast rate until the blood pressure had fallen to within 10 mm Hg of the desired systolic level. By this means we obtained a rapid reduction in pressure in every case. Besides being an advantage in probably helping to avoid tachyphylaxis there was also a minimal delay in getting the operation under way. It has been said that there is a danger of acute circulatory failure during the induction of hypotension (Scurr, 1955) and no doubt the more rapid the fall the more likely this would be. However, provided the blood pressure is kept under constant observation throughout this period, although wide differences in susceptibility occur, these are noticed immediately and the appropriate slowing of the drip quickly brings the fall under control.

The type of resistance just described during the induction of hypotension by the intravenous route must be distinguished from the inherent resistance to the maintenance of hypotension in certain individuals, particularly in the young and robust group (Enderby and Pelmore, 1951). To achieve satisfactory and stable hypotension in this type of patient various other agents have been used to supplement trimetaphan. Thus, Anderson and McKissock (1953) used procaine amide in the manner described by Mason and Pelmore (1953) to compensate for inadequate results obtained with hexamethonium. Scurr and Wyman (1954) added pentamethonium and Loew (1954) used pendiomide. In addition to the use of a second hypotensive agent, various other measures have been advocated to assist in lowering the blood pressure in resistant subjects. Thus, the application of negative pressure to the legs has been used by Saunders and his associates (Saunders, 1952; James, Coulter and Saunders, 1953) to reduce the effective circulating blood volume by trapping blood in the veins of the lower extremities. This is a modification of the usual method of producing venous pooling by posture. It is a valuable aid wherever possible to position the patient with the operation site in a nondependent position and in our cases this is done after the patient is anaesthetized and before hypotension is induced. We are, however, strongly of the opinion that it is unjustifiable in any circumstances to use a head up position and all patients in the present investigation were in a strictly horizontal or slightly head down position. Deepening the level of anaesthesia can also be employed to aid in the reduction of blood pressure, but in general we believe that this is unwise unless anaesthesia has become unnecessarily light.

If a satisfactory level is not obtained before the operation is started or if the blood pressure is allowed to "escape" after a satisfactory initial fall,

large quantities of trimetaphan may be given with rather inadequate results. It is therefore very important to achieve the desired level of hypotension before the initial skin incision is made. As well as an undesirable rise in blood pressure which may subsequently be difficult to get under control, this mistake may introduce another factor of considerable importance, namely excessive bleeding in the early stages of the operation. If this occurs at a time when the autonomic ganglia are incompletely blocked a compensatory vasoconstrictor mechanism may be called into play which may be difficult to overcome. Further, the loss of blood will undermine the confidence of the operator in the procedure. It also adds another complicating factor which is highly undesirable, namely lowering the circulating blood volume, a state which is poorly tolerated at low pressures.

Adrenaline sensitization. In three of our cases we were unable by the use of Trophenium alone to maintain a satisfactory level of hypotension. Thus, the systolic pressure showed an initial rapid fall to between 70 and 80 mm Hg and although slowing of the drip rate was not excessive the pressure began to rise and despite repeated speeding up of the drip the systolic pressure rose to the region of 80–110 mm Hg. Thereafter throughout the period of administration of Trophenium the blood pressure was uninfluenced by wide variations in drip rate and even by the administration of 50–100 mg of the undiluted drug intravenously. Zaimis (1955, 1956) has shown that this diminished effect on blood pressure following subsequent doses of ganglion blocking drugs is due not to a lowered sensitivity of the ganglionic synapse but to a sensitization of the effector cells to adrenaline and noradrenaline, an effect more apparent under such a condition as surgical anaesthesia. She points out that this decreasing response from the blood pressure could be shown clinically to be due to a peripheral action of adrenaline by the administration of an anti-adrenaline substance but for the practical difficulty that none of those at present available is a powerful antagonist of the intrinsically liberated sympathomimetic amines. In addition, an anti-adrenaline substance used for this purpose would need to have a short duration of action. It is interesting that, in these three patients, as with similar cases receiving trimetaphan where the blood pressure became fixed, the pulse rate increased and there was marked pallor of the face and wide dilatation of the pupils indicating an increase in peripheral sympathetic tone. While the pupils are occasionally large during the administration of hypotensive agents, the size varied considerably, most, however, showing some degree of dilatation.

This development of tachyphylaxis due to sensitization of the peripheral receptors to adrenaline and noradrenaline may be enhanced by the gradual reduction of the blood pressure with ganglion blocking drugs. Under these conditions reflex pressor activity would increase the amounts of adrenaline and noradrenaline being liberated, as would operative stimuli and haemorrhage occurring before ganglion blockade had lowered the blood pressure to hypotensive levels.

Swinging blood pressure level. It has been noted that in a few patients difficulty was met in maintaining a steady level of systolic blood pressure with Trophenium as has been described with trimetaphan (Little, 1954). This is, no doubt, due largely to the fact that some patients are more susceptible to these drugs than others and develop little or no tolerance during their administration. Another factor of importance when a drug with a very short duration of action is being given is accurate control of the rate of administration. Thus, while in most cases the drip was easily regulated by the ordinary screw clip, occasionally extraneous factors such as compression or movement of the arm by one of the surgical team could cause an alteration in the drip rate. In eight cases a polythene catheter was inserted into an arm vein and the hypotensive agent given at an accurately controlled rate from a motor driven syringe. This method was, however, unnecessarily cumbersome and little trouble was experienced with the drip if the needle was inserted into the cephalic vein on the radial side of the wrist and the arm carefully positioned before the hypotension was induced. The concentration of Trophenium in saline was also of importance in determining the stability or otherwise of the blood pressure during the period of controlled hypotension. It was found that with the use of dilute solutions, less than 2 mg/ml, swinging of the pressure was more likely

to occur. This may have been in part related to the volume of saline employed.

Time of recovery of blood pressure. The duration of action of the hypotensive drug is a primary factor in determining the time taken for the blood pressure to return to normal after the administration has been stopped. There are, however, many other factors; thus, recovery time will be affected by the level of hypotension maintained (table VIII), its duration and the total quantity of drug used (table IX). Individual variations in patients such as age (table V), general condition (table VI) and pre-operative level of blood pressure (table VIII), surgical factors including the nature of the operation, its duration, blood loss, position of the patient and body temperature (Zaimis, 1955), and anaesthetic factors such as agent, duration (table IX), depth of anaesthesia, may all influence in some degree the length of time before restoration of the blood pressure to normal level. Finally, in the postoperative period, recovery from hypotension may be affected by administration of drugs such as atropine and neostigmine, the return of spontaneous breathing, the replacement of blood, tilting of the table, and changes in position of the patient. From table IX it would appear that the recovery time in the two series is closely related to the duration of the operation, anaesthetic and infusion, but not to the total dose of hypotensive agent used which is remarkably similar in the two series.

Complications. A review of 381 thoracotomies carried out on 363 patients for pulmonary tuberculosis has been made with the object of relating the incidence of postoperative haemorrhage to the use of hypotensive agents (Tough, 1956). In 268 of these, various hypotensive agents have been employed including hexamethonium, trimetaphan, Trophenium, and in the others similar operations were carried out under the same type of general anaesthesia but without the use of a hypotensive drug. The incidence of haemorrhage in the whole series was 10.2 per cent, that in the group in which hypotension was used being 10.4 per cent and in the group without hypotension 9.7 per cent. It was concluded that in this series the use of a hypotensive agent in conjunction with anaesthesia had no significant effect on the incidence of postoperative haemorrhage.

Due to their action in blocking parasympathetic visceral ganglia, all drugs which block autonomic ganglion transmission depress motor activity of the gastro-intestinal tract and urinary bladder. This action has been utilized in the employment of hexamethonium in the treatment of peptic ulcer (Kay and Smith, 1950). Constipation, paralytic ileus and urinary retention, therefore, constitute possible complications following the use of ganglion blocking drugs. The occurrence of these in the published clinical reports are, however, rare and where meteorism was observed to occur, it was thought likely that it was due to other causes (Holmes, 1956), as Douthwaite and Thorne (1951) found that the maximal duration of action of hexamethonium on the gut was 6 hours. In view of the fact that Trophenium is chemically related to atropine, which also possesses these effects on intestinal and urinary motor function, it might be expected that complications involving atony of these organs were likely to be enhanced by this agent. However, as has been already described in the pharmacological report, the atropine-like side actions of Trophenium are negligible. It might therefore be expected that complications of this nature would be no more frequent with Trophenium than with other ganglion blocking agents.

In two cases in the thoracic series, patients suffering from diabetes mellitus were given Trophenium to induce hypotension. Griffiths (1953) has shown that there is a tendency for the blood sugar to fall following the administration of hexamethonium. The hypoglycaemia may become very profound without being apparent since the usual symptoms of the condition, namely sweating, palpitations, restlessness and anxiety, are due to sympathetic and adrenal discharge and are prevented by ganglionic blockade. In our cases a continuous infusion of 5 per cent glucose solution was given throughout the period of Trophenium administration. Tachycardia did not occur. There was no unusual effect on the diabetic condition observed during the postoperative period.

SUMMARY AND CONCLUSIONS

Preliminary trials with a new ganglion blocking agent, Trophenium, to produce controlled hypo-

tension during general anaesthesia and surgery are described.

The drug has been employed on 76 occasions during general surgical and thoracic operations where it was considered that a reduction in bleeding would be of benefit to the patient.

Trophenium has been found to be an effective hypotensive agent when administered by intravenous drip infusion, a satisfactory stable level of blood pressure being obtained in the majority of cases. In six cases, however, difficulty was experienced in maintaining a steady level of hypotension, frequent alterations in drip rate being accompanied by swinging of the pressure.

All patients in the present investigation were in a horizontal or slightly head down position. Posture depended almost entirely on the nature and site of the surgical procedure and only to a minor degree was it utilized as an aid in producing hypotension. Despite this, in all but three cases an adequate hypotensive level was achieved.

There was one death in the series. This occurred 26 days after operation and appeared to be unrelated to the induced hypotension. The non-fatal postoperative complications are tabulated and discussed.

From this trial we believe that Trophenium is a satisfactory drug for the production of controlled hypotension during surgery. As its hypotensive action is of short duration and appears to be due to a specific ganglion blocking effect it is readily controllable by alterations in the drip rate. We consider that it merits an extended clinical trial.

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BOOK REVIEW

Surgery of the Anus, Anal Canal, and Rectum. By E. S. R. Hughes. Published by E. and S. Livingstone, London. Pp. 300; 276 illustrations. Price 50*s*.

This is a book which is concise, full of practical points, and contains the carefully considered views of the author.

The section on anatomy is particularly good as is also the historical survey.

There is a chapter on anaesthesia by Dr. G. Houseman, F.F.A.R.C.S., F.F.A.R.A.C.S., which is clearly written but rather short. It is stated that general anaesthesia has almost completely replaced spinal analgesia. Whilst the reviewer does not disagree entirely with the author, this does seem a rather sweeping statement. However, the author is doubtless referring to his own practice and does not intend that this shall be taken to represent worldwide opinion.

There are two small points which might be criticized in this admirably clear chapter: gallamine triethiodide is written in capitals, and the patient is described as "Lying vertically on the left side". This is a little confusing to the reader. The use of local anaesthesia and nerve block for haemorrhoidectomy could have received more emphasis, but there is a good section on sacral infiltration by Dr. Russell Cole, F.F.A.R.C.S. However, this is a book on surgery, not anaesthesia, and it would be unfair to be too critical. Dare the writer suggest that in future editions, and he hopes there will be many, the use of nerve block in combination with thiopentone intravenously be given more space.

Frankis Evans

Brit. J. Anaesth. (1957), **29**, 358

THE INFLUENCE OF MECAMYLAMINE ON THE ACTION OF CERTAIN OTHER GANGLIONIC BLOCKING AGENTS*

BY

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RECENT advances in pharmacological knowledge and pharmaceutical techniques have produced a large series of new drugs of low toxicity and few side effects. These advantages together with more specific properties allow their continued use over long periods in the management of chronic disease. At first sight few of these drugs are of direct interest to anaesthetists and consequently tend to be largely ignored in the specialty. Experience has shown, however, that a number, unconnected with anaesthesia, are capable of modifying profoundly the normal response to anaesthesia should surgery have to be undertaken during their administration. In particular, the dangers associated with the cortisone group of drugs are sufficiently serious to justify the warning given (Wood-Smith and Payne, 1955) that all patients about to undergo surgery should be specifically questioned about treatment with cortisone. Shortly after cortisone was introduced into clinical practice it could be assumed with a fair degree of certainty that any patient suffering from chronic inflammatory disease was likely to have had one or more courses of cortisone therapy so that anaesthetists were forced to modify their techniques accordingly.

The use of mecamylamine in the treatment of hypertension (Freis, 1955) has brought further problems. Chemically, 3-methyl-aminoisocamphane hydrochloride (Stone et al., 1956), this drug is a ganglion blocking agent which is stored in the tissues (Milne et al., 1957) and not readily excreted. In addition, it is rapidly and apparently completely absorbed from the alimentary canal and therefore can be conveniently given by mouth. For these reasons it is very suitable for the long term management of the hypertensive patient. Mecamylamine, however, is not without side effects; constipation and gastrointestinal atony have been reported (Freis, 1955) and experimental work has indicated that in the cat the action of mecamylamine is potentiated by the accumulation of carbon dioxide (Payne and Rowe, 1957). The experiments to be described emphasize a further difficulty; if hexamethonium is given to a cat previously treated with mecamylamine, neuromuscular block results. It remains to be shown that these observations apply to man, but it would be foolish to ignore them in the absence of that proof.

METHOD

Five healthy cats were used for the experiments. After induction with ethyl chloride and ether, anaesthesia was established with intravenous chloralose (80 mg/kg). A tracheal cannula was inserted and artificial respiration established by means of an ' Ideal ' respiration pump. The right external jugular vein was cannulated for the purpose of intravenous injections and the blood pressure was recorded directly from the left carotid artery using a mercury manometer. The tendon of the right tibialis anterior muscle with its nerve supply was isolated after the manner described by Brown (1938). The tendon was attached to a flat steel spring myograph recording on a smoked drum and the nerve was stimulated through shielded platinum electrodes. A supramaximal square wave pulse of 0.5 m.sec duration was used with a strength of 1–3 volts at 10-second intervals. At varying periods of time after the administration of intravenous mecamylamine, hexamethonium was given and the effects on the muscle twitch and blood pressure recorded. In one instance trimetaphan camphorsulphonate (Arfonad) was substituted for hexamethonium.

* Work done in Department of Pharmacology, Royal College of Surgeons of England, London.

RESULTS

In five cats previously given mecamylamine the intravenous injection of hexamethonium was followed by neuromuscular block. The quantitative relationships between the factors involved are set out in table I. Normally the dose of hexamethonium employed in these experiments has no effect on the muscle twitch, as shown in figure 1A.

In four of the five cats mecamylamine block was preceded by potentiation of the twitch (fig. 2A) which persisted for several minutes before signs of neuromuscular block ultimately became apparent. In the fifth cat the absence of potentiation (fig. 1B) may have been due to the earlier administration of hexamethonium.

The competitive nature of hexamethonium block after mecamylamine is shown in figures 1, 2 and 3. Initial potentiation is absent and there is no evidence of muscle fasciculation nor spontaneous contractions. The rate of onset and duration

TABLE I

Percentage depression of neuromuscular activity in cats given hexamethonium after preliminary injections of mecamylamine.

Weight of cat (kg)	Dose of mecamylamine (mg/kg)	Time between drugs (min)	Dose of hexamethonium (mg/kg)	Depression of twitch (%)
4.2	40	320	2	70
2.9	40	300	2	40
3.5	50	200	3	63
3.4	10	100	10	95
2.7	10	50	4	80

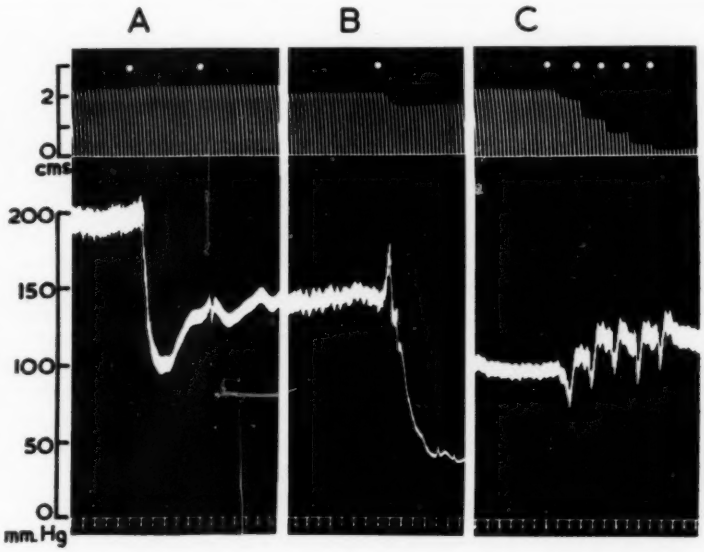

FIG. 1

Records of tibialis anterior contraction and blood pressure in a cat. Time interval 30 sec.

Hypotension without neuromuscular block after intravenous hexamethonium (A). 250 minutes later, marked hypotension and slight neuromuscular block after 10 mg/kg mecamylamine (B). 90 minutes later nearly complete muscular block without further hypotensive effect after 10 mg/kg hexamethonium (C).

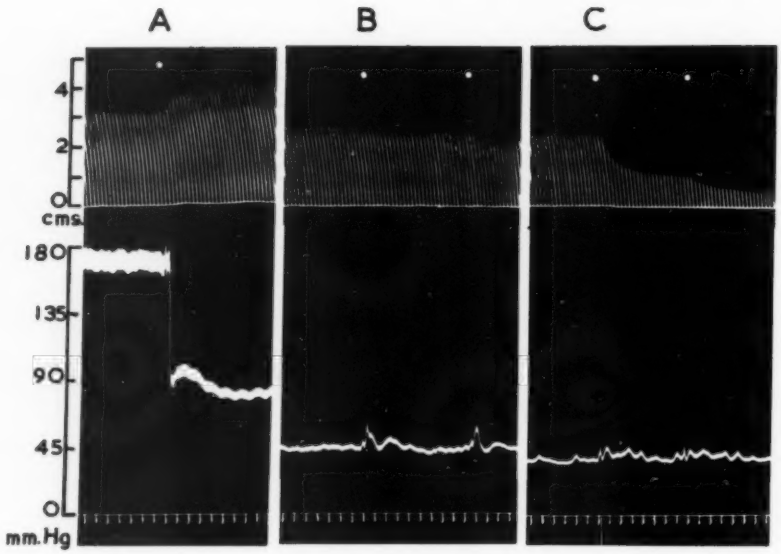

FIG. 2

Records of tibialis anterior contraction and blood pressure in a cat.
Time interval 30 sec.

Potentiation of neuromuscular twitch and hypotension after 10 mg/kg mecamylamine (A). 30 minutes later, neuromuscular block without further hypotension after trimetaphan (B). First injection of trimetaphan (not shown) lowered blood pressure from 80 mm Hg to 45 mm Hg. Finally, after a further 20 minutes, neuromuscular block without further hypotension after hexamethonium (C).

of action are similar to that seen with gallamine in a series of unpublished experiments.

The neuromuscular block produced by trimetaphan camphorsulphonate closely resembles that of hexamethonium but is much weaker (fig. 2B).

The influence of carbon dioxide on the combined effects of hexamethonium and mecamylamine is obvious from figure 3. The neuromuscular block was potentiated and the blood pressure further reduced when the animal was ventilated with 10 per cent carbon dioxide.

In contrast to its action at the motor endplate hexamethonium had no further effect on blood pressure after a fall had been achieved with mecamylamine. Trimetaphan camphorsulphonate, however, lowered the blood pressure from 80 mm Hg to 45 mm Hg in the only experiment in which the drug was used, but additional doses had no further effect.

DISCUSSION

One of the features of the methonium compounds is the manner in which their pharmacological properties are altered by the reduction in length of the carbon chain connecting the quaternary nitrogen atoms. In particular, the neuromuscular blocking action which is marked with decamethonium is almost negligible if hexamethonium is substituted; with this drug the head-drop test in rabbits is positive only when large doses are employed (Paton and Zaimis, 1952). There is no evidence that with the doses used in this series hexamethonium will produce neuromuscular block either in the cat (fig. 1A) or in man in normal circumstances. The present study shows, however, that if such doses are preceded by intravenous mecamylamine a considerable degree of neuromuscular block will result.

Mecamylamine itself possesses a weak neuro-

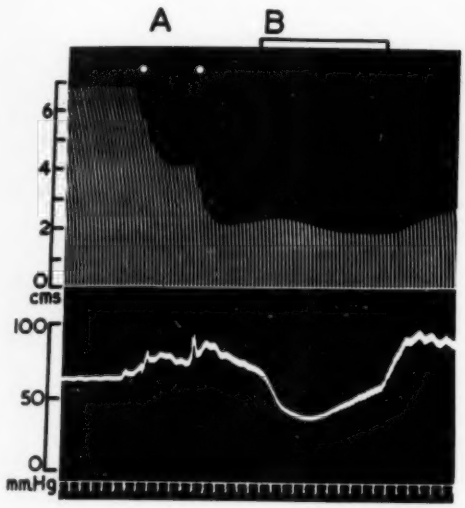

FIG. 3

Records of tibialis anterior contraction and blood pressure in a cat previously given 40 mg/kg mecamylamine. Time interval 30 sec.

After 320 minutes, neuromuscular block produced by two injections of hexamethonium without further hypotension (A); potentiation of neuromuscular block and hypotension by inhalation of 10 per cent carbon dioxide (B).

muscular blocking action (Stone et al., 1956) and it may be that hexamethonium merely potentiates this effect. Such potentiation is known to occur when cats previously given mecamylamine are exposed to carbon dioxide (Payne and Rowe, 1957). It was also shown that the increase in neuromuscular block was associated with a raised plasma level of the drug and it was suggested that carbon dioxide acts by mobilizing mecamylamine from the tissues. It seems unlikely that hexamethonium can act in this way as it can neither readily penetrate the cell membrane, nor has it any demonstrable ability to alter the plasma pH.

The evidence in favour of a direct action by hexamethonium is more convincing. The neuromuscular block observed in the present study is competitive in nature and similar to that reported by Paton and Zaimis (1952) in their detailed account of the properties of hexamethonium. It differs from mecamylamine block in several respects; there is no initial increase in the amplitude of the muscle twitch, the block develops faster and recovery is more rapid. In one respect, however, it resembles that of mecamylamine. Both blocks respond to carbon dioxide by further depression of neuromuscular activity. The significance of this observation is difficult to assess because carbon dioxide antagonizes the blocking action of certain other members of the methonium series, decamethonium and suxamethonium, as well as that of gallamine (Payne, 1957), and it might be expected that hexamethonium would react in the same way.

Acetylcholine is essential for the normal transmission of impulses at the motor endplate and if its release is impeded it is possible that the weak block produced by hexamethonium may be potentiated. According to Crawford (personal communication), there is some evidence to suggest that mecamylamine does inhibit the normal synthesis of acetylcholine. If this is so the block obtained could be explained by the relative increase in the amount of hexamethonium available to compete with acetylcholine.

Even if it is accepted that mecamylamine is not directly responsible for the neuromuscular block it must be agreed that the block is influenced by the drug. Mecamylamine may modify the motor endplate in such a way that the receptor sites can accommodate hexamethonium to the exclusion of acetylcholine. Evidence that mecamylamine can disturb the normal process at the motor endplate is forthcoming from the work of Zaimis and her colleagues (personal communication), who have shown that when suxamethonium is given to fowls previously treated with mecamylamine the normal response of neck retraction is changed to head-drop and the rigid extension of the limbs is replaced by flaccid paralysis. There is in fact a shift from depolarization block to competition block.

Personal experience, both clinical and experimental, suggested that trimetaphan camphorsulphonate extended the duration of the neuromuscular block produced by gallamine. This was attributed to the lowered renal blood flow and the subsequent reduction in the excretion rate of gallamine. A weak curare-like action has previously been reported in dogs given trimetaphan (Randall

et al., 1949). This was interpreted as evidence of a reduced blood flow through the limb muscles subsequent to a fall in arterial pressure rather than to a direct action at the motor endplate. It is apparent, however, that in certain circumstances trimetaphan camphorsulphonate is capable of a weak neuromuscular blocking action (fig. 2B) which is independent of the state of the blood pressure.

Whatever the mechanisms involved it is certain that if similar changes can be demonstrated in man the potential hazards of anaesthesia will be increased. Admittedly, the factor of species difference introduces an element of doubt, but until definite evidence is forthcoming, it is surely wise to avoid the use of such combinations of drugs except under strictly controlled conditions where the risk to the patient is minimized and where the results can be carefully assessed.

SUMMARY

Hexamethonium is shown to produce neuromuscular block in cats previously given mecamylamine.

Trimetaphan camphorsulphonate is shown to have a similar but less marked action at the motor endplate under the same conditions.

The mechanism by which mecamylamine modifies the action of these ganglion blocking agents is discussed.

Attention is drawn to the potential risk if similar influences prevail in man.

ACKNOWLEDGMENTS

I am indebted to Professor W. D. M. Paton, F.R.S., for facilities to carry out this work and for his advice and criticism.

My thanks are also due to Miss Dawn Hedges and Mr. D. Green for technical assistance, and to Dr. J. F. Merry of Messrs. Merck Sharp and Dohme for supplies of mecamylamine.

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EDITORIAL *continued from page* 341

all experiences" he has both the knowledge and ability to use it. He should be, therefore, a good teacher and a good demonstrator. He will thus gain interest in a wider application of his powers and as Dr. Flagg says, "He will develop more respect for the integrity of normal physiology. He will become more conservative in subordinating these normal procedures to depressive and lethal drugs." Thus we may expect all round benefit to accrue to the student, the anaesthetist and the general public whom they serve.

It is hoped that we may be able to publish Dr. Flagg's communication later, possibly in an Educational Number.

Brit. J. Anaesth. (1957), **29**, 363

ELECTROCARDIOGRAPHIC STUDIES DURING ENDOTRACHEAL INTUBATION AND INFLATION OF THE CUFF

BY

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INTRODUCTION

THE electrocardiogram was introduced to clinical medicine in 1915, and in 1918 it was first used to study the patient under anaesthesia (Krumbhaar, 1918; Heard and Strauss, 1918).

The vagal effects of anaesthetic drugs have since been studied in many papers on electrocardiography during anaesthesia (Lennox et al., 1922; Wachsmuth and Eismeyer, 1928; Ward and Wright, 1929; Hill, 1932a, b; Kurtz et al., 1936) but it was not until 1940 that electrocardiographic effects of intubation were investigated (Reid and Brace, 1940). In 10 of the 35 cases which were studied under cyclopropane anaesthesia there were indisputable reflex effects upon the heart. The e.c.g. changes included extrasystoles (auricular and ventricular), delayed conduction time and slowing of the heart.

Cases of cardiac arrest due to vagal reflexes fired off by the insertion of pharyngeal or endotracheal tubes have been described (Waters and Gillespie, 1944; Nosworthy, 1948; Gillespie, 1948; Smith and Nolan, 1950; Scurr, 1950; Dale, 1952). These accidents apparently were not confined to cyclopropane or thiopentone anaesthesia but might occur with all types of general anaesthesia.

Burstein and others have extensively investigated the e.c.g. disturbances during intubation (Burstein et al., 1950a, b; 1951; Peters et al., 1951; Arcuri et al., 1953; Rosner et al., 1953; Dance et al., 1956). Under various anaesthetics over 60 per cent of patients showed transitory changes consisting of sinus tachycardia, sinus bradycardia, premature ventricular contractions, ventricular tachycardia and bigeminal ventricular tachycardia, auricular fibrillation, nodal rhythm, heart block, increase in the PR interval, decrease in voltage of the T wave and depression of the ST segment.

Insufficient depth of anaesthesia, hypoxia and hypercarbia were associated with these disturbances.

When general anaesthesia was complemented by topical analgesia of the pharynx and larynx with 5 per cent aqueous solution of cyclaine, e.c.g. disturbances occurred in only 14 per cent of cases at the time of intubation.

When hexobarbitone sodium was used for induction it was found that the incidence of cardiac arrhythmias on intubation was less than 1 per cent but without hexobarbitone there was an incidence of 28 per cent.

It was demonstrated (King et al., 1951) that direct laryngoscopy or tracheal intubation under light general anaesthesia was capable of producing decided circulatory effects characterized by a rise in blood pressure and an increase in heart rate.

It was shown (Johnstone, 1952) that it was possible to intubate a patient without causing any cardiac upset if moderately deep cyclopropane anaesthesia was used. As a result of observations carried out during 2,000 endotracheal intubations it was suggested that cardiac arrythmias which follow intubation were due either to vagal release following the escape of anaesthetic agents from the lungs or to partial asphyxia as the result of bronchospasm precipitated by the insertion of tubes into inadequately anaesthetized patients.

In a series of 52 cases, nodal rhythm occurred immediately after intubation in 1 case (Fisher and Windsor, 1952). Of 41 patients studied in another series, 1 developed bigeminal rhythm and 2 a nodal rhythm during intubation (Converse et al., 1952).

In a series of 230 cases (Stephen et al., 1953) 20 showed the following e.c.g. changes after insertion of the endotracheal tube: shortening of the PR interval in 1 case, nodal rhythm in 2 cases,

decreased QRS voltage in 1 case, depressed T wave in 8 cases, premature ventricular contractions in 6 cases and bigeminal rhythm in 2 cases. It was found that cardiac arrhythmias were less frequent with gallamine than with the other relaxants which included tubocurarine, suxamethonium and benzoquinonium.

It was shown (Phillips, 1954) that suxamethonium used for endotracheal intubation produced cardiac irregularities including auricular standstill, nodal rhythm, ventricular extrasystoles and bradycardia as low as 40 beats a minute followed by tachycardia as high as 140 beats a minute.

In e.c.g. studies carried out during 110 intubations under cyclopropane anaesthesia changes in cardiac rhythm were observed in 4 instances (Denson and Joseph, 1954). Ventricular rhythm occurred simultaneously or within 3 seconds of the introduction of the endotracheal airway, but in each instance the presence of asphyxia could not be ruled out.

It was demonstrated (Johnstone, 1955) that ventricular extrasystoles occurred in 2 of 25 patients intubated under gallamine, and in 7 of 25 patients intubated under tubocurarine, but no such changes were observed in 25 cases intubated under suxamethonium. One patient developed a deep depression of T2 during intubation under gallamine and persisted for 7 minutes until normal respiration returned.

In an e.c.g. study of 219 patients undergoing surgical anaesthesia with various agents the most common sequel to intubation was tachycardia (Horton, 1955). This occurred in 181 cases, in 3 there was no change and in the remaining 35 there was slowing of the pulse rate. Extrasystoles were seen at or after intubation in 18 cases. The ectopic beats were ventricular in 14, AV nodal in 1, and auricular in 3 cases, but no marked evidence of either cardiac irritation or inhibition was seen.

In a study of 121 patients who were intubated following induction with thiopentone and relaxation with tubocurarine it was found that intubation produced arrhythmias in 9 per cent of well oxygenated and in 36 per cent of hypoxic patients (Jacoby et al., 1955).

These various e.c.g. changes, some trivial and some of more serious import stimulated us to study in detail all the components of the e.c.g. during intubation and inflation of the cuff in a series of 40 cases.

MATERIAL AND METHODS

Of the 40 cases, 19 were females and 21 males. Their ages ranged from 18 to 71 years and their weights ranged from 6 st. 6 lb. (40.9 kg) to 14 st. 4 lb. (89 kg). Thirty-seven were normotensive and 3 were hypertensive. All had a normal preoperative haemoglobin concentration.

Premedication consisted of various drug and dosage combinations, but the majority received either papaveretum or pethidine and scopolamine, and 13 received chlorpromazine in addition.

All were induced with 2½ per cent thiopentone injected slowly, the dose ranging from 175 mg to 500 mg. Prior to intubation all received a relaxant drug; 30 received gallamine in a dose ranging from 80 to 140 mg, 6 received suxamethonium in a dose ranging from 5 to 100 mg, and 4 received tubocurarine in a dose ranging from 20 to 35 mg.

Prior to intubation 37 received pethidine intravenously in a dose ranging from 50 to 100 mg and of these 11 received hexamethonium iodide in addition, in a dose ranging from 30 to 100 mg (table I).

Standard lead e.c.g.s were taken before and after induction of anaesthesia, after the relaxant and after the pethidine and the hexamethonium (when these were used), during intubation, during inflation of the cuff and after inflation of the cuff. These were recorded on an Elmquist triplex machine. Prior to intubation each patient was ventilated with 100 per cent oxygen for 3-5 minutes. This was done to avoid hypoxia and CO_2 accumulation on the one hand, and, on the other, to allow the relaxant and the pethidine and the hexamethonium (in the cases in which these drugs were used) to have time to circulate and to take effect. Each patient was ventilated with 100 per cent oxygen during inflation of the cuff again to avoid hypoxia and CO_2 accumulation and also to assess when the cuff was adequately inflated. The size of the tube chosen was the largest that would pass without trauma, and to facilitate its introduction a metal stylet was used. Blood pressure and pulse rates were recorded before and after induction, before intubation, on intubation,

TABLE I
Results

Case No.	Sex	Age	Weight		Chlorpromazine	Thiopentone	Relaxant	Dose	Pethidine	Hexamethonium	B.P. response
			st	lb	mg	mg		mg	mg	mg	
1.	M	57	10	6		450	gallamine	120	50	50	—
2.	F	51	8	2	50	200	suxamethonium	50			+
3.	M	19	11	9		500	gallamine	140	100	100	—
4.	F	68	13	6		450	,,	120	50	50	—
5.	M	54	9	8	50	400	suxamethonium	50	50		+
6.	F	54	10	13		500	gallamine	80	50		+
7.	M	53	9	2		500	,,	120	75		+
8.	M	55	9	10		300	,,	120	50		+
9.	F	19	6	6		300	,,	80	50	50	—
10.	M	30	9	6		500	,,	120	50	100	—
11.	F	41	8	10		400	,,	100	75		+
12.	M	59	14	4		500	,,	120	50		+
13.	F	46	11	2		500	,,	140	100		+
14.	F	34	10	2	50	300	,,	120	100		+
15.	F	47	9	8	50	250	suxamethonium	50			+
16.	M	26	11	0	50	250	,,	100	50		+
17.	M	41	9	11		500	gallamine	140	100		+
18.	F	51	7	4	50	200	suxamethonium	100	50		+
19.	F	65	8	11		250	gallamine	120	50	50	—
20.	M	53	11	0		400	,,	140	100		—
21.	M	21	9	5		500	,,	140	100	100	—
22.*	M	42	10	4	50	300	,,	140	100		+
23.	F	45	10	9		450	,,	140	100		—
24.*	F	51	8	6		400	,,	120	50	50	—
25.	F	41	12	2		500	,,	140	75		—
26.	F	38	7	13		300	,,	120	75	50	—
27.	M	47	9	8		300	,,	120	50	30	—
28.	M	28	10	10		500	,,	140	100		+
29.	M	40	11	0	50	200	tubocurarine	35			+
30.	M	31	9	4	50	300	gallamine	120	50		+
31.	F	33	7	10	50	175	tubocurarine	30	50		+
32.	M	44	11	4	50	500	,,	20	50		+
33.*	M	62	10	10		300	gallamine	120	50		—
34.	F	57	11	0		500	,,	140	75		+
35.	F	71	8	1		300	,,	120	50		+
36.	M	53	9	12		450	,,	140	100		—
37.	F	63	9	11		350	,,	120	50		+
38.	M	48	9	4		500	,,	140	100	100	—
39.	F	65	6	7	25	200	tubocurarine	30	50		+
40.	M	18	9	10	50	500	suxamethonium	75	50		+

**Hypertensives:*
No. 22 B.P. 290/170.
No. 24 B.P. 200/105.
No. 33 B.P. 210/130.

Pressor Response:
\+ = 10–30 mm Hg
\+ + = 31–50 mm Hg
\+ + + = 51–70 mm Hg
\+ + + + = 71–90 mm Hg

TABLE II
P Wave Changes

Case No.	On intubation	On inflation of cuff	First reading after inflation of cuff
1	No change	No change	P2 −1.5 mm
15	,,	P1 −1.0 mm	Change disappeared
18	,,	P2 and P3 −1.5 mm	,, ,,
20	,,	P2 +1.0 mm	,, ,,
22	P2 −1.0 mm	P2 change persisted	P2 +2.0 mm
36	P1 −1.0 mm	Change disappeared	No change
38	No change	P1, 2, 3 disappeared (nodal rhythm)	Nodal rhythm

+ = Increase in height of P wave. − = Decrease in height of P wave.
Case No. 38 is illustrated in figure 1, Case No. 15 in figure 2, and Case No. 36 in figure 5.

on inflation of cuff, and after inflation of the cuff.

In addition to changes in blood pressure and pulse rate, changes in the various components of the e.c.g. were also sought. These included changes in the P wave, PQ, QRS and QT intervals, QRS voltage, axis rotation and ST and T wave changes. Practically every case showed minor changes in all the components of the e.c.g. but of the voltage changes only those of 1 mm or more were recorded. In one case (No. 29) ventricular extrasystoles were present prior to intubation, but these disappeared after intubation.

The first and second e.c.g. tracings after inflation of the cuff were also examined for changes in the various components. The first was usually under 5 minutes and the second under 10 minutes after inflation. Changes occurring in these tracings were only reported in the tables where it was felt that the changes were in fact due to intubation and inflation of the cuff.

In themselves none of the QRS interval changes was significant, but as the QRS interval forms part of the QT interval it is important to consider even minor changes in the QRS interval when deciding whether or not there is a significant change in the QT interval.

All the QTc intervals (i.e. QT intervals corrected for pulse rate) were within normal limits, but those showing a change of 0.04 second or more on intubation or inflation of the cuff are listed in table IIIA.

DISCUSSION

Pressor Response.

No pressor response to intubation or inflation of the cuff was observed in any of the 11 cases receiving hexamethonium prior to intubation, suggesting that this drug produces an effective autonomic blockade. The dosage ranged from 3 to 10 mg per stone (6.3 kg) body weight.

Chlorpromazine on the other hand when given as premedication in a dosage of approximately 5 mg per stone (6.3 kg) body weight failed to prevent a pressor response in the 13 cases in which it was used. Case no. 16 (table I) illustrates how severe the pressor response can be under light anaesthesia in the absence of hexamethonium.

Pulse Rate.

The pulse rate increased by more than 10 beats per minute on intubation or inflation of the cuff in 22 of the 40 cases. Seven of the 11 cases receiving hexamethonium, and 7 of the 13 cases receiving chlorpromazine showed this increase (tables I and III).

In one case (no. 5) a decrease of more than 10 beats per minute occurred on intubation.

P Wave Changes.

These occurred in 7 cases (table II), 2 (nos. 22, 36) on intubation when the P wave was depressed; 4 on inflation of the cuff (nos. 15, 18, 20, 38); and 1 on the first reading after inflation of the cuff (no. 1). In case no. 38 the P wave disappeared with the establishment of nodal rhythm on inflation of the cuff.

PQ, QRS and QT Intervals.

The PQ intervals (table III) varied, but with the exception of case no. 38, the changes were related to alterations in pulse rate as would be expected, i.e. the faster the pulse rate the shorter the PQ interval, and were of no significance.

The QRS intervals changed but not sufficiently to be significant.

TABLE III

PQ, QRS and QTc Intervals

Case No	Pulse rate/minute				PQ interval in seconds			QRS interval in seconds			QTc interval in seconds		
	Before intubation	On intubation	On inflation	After Inflation	Before intubation	On intubation	On inflation	Before intubation	On intubation	On inflation	Before intubation	On intubation	On inflation
1.	120	120	125	120	0.14	0.12	0.12	0.08	0.06	0.06	0.34	0.34	0.30
2.	86	83	86	68	0.20	0.20	0.18	0.08	0.08	0.06	0.40	0.40	0.40
3.	120	120	136	120	0.18	0.18	0.16	0.08	0.06	0.06	0.34	0.30	0.32
4.	109	100	125	109	0.14	0.16	0.18	0.04	0.04	0.04	0.36	0.38	0.34
5.	107	94	130	115	0.14	0.14	0.14	0.04	0.04	0.04	0.32	0.32	0.32
6.	86	100	109	110	0.18	0.14	0.14	0.08	0.08	0.08	0.42	0.38	0.38
7.	120	120	130	120	0.14	0.14	0.14	0.08	0.08	0.08	0.30	0.28	0.26
8.	92	86	88	86	0.14	0.12	0.14	0.04	0.06	0.06	0.28	0.32	0.30
9.	120	133	130	120	0.16	0.18	0.18	0.05	0.04	0.04	0.30	0.30	0.30
10.	86	100	83	100	0.13	0.15	0.14	0.06	0.06	0.04	0.36	0.32	0.36
11.	160	172	172	172	0.12	0.12	0.12	0.06	0.06	0.06	0.28	0.24	0.24
12.	120	133	136	120	0.16	0.16	0.16	0.08	0.08	0.08	0.26	0.34	0.30
13.	100	100	120	92	0.16	0.15	0.15	0.06	0.06	0.06	0.34	0.32	0.30
14.	125	143	167	143	0.12	0.14	0.14	0.06	0.06	0.06	0.22	0.24	0.24
15.	115	120	125	103	0.14	0.12	0.14	0.06	0.04	0.04	0.32	0.32	0.34
16.	136	130	130	143	0.16	0.16	0.18	0.06	0.08	0.08	0.24	0.28	0.26
17.	133	133	120	133	0.14	0.14	0.15	0.04	0.06	0.06	0.26	0.24	0.26
18.	111	111	150	86	0.16	0.16	0.14	0.06	0.06	0.04	0.28	0.24	0.24
19.	100	94	107	100	0.14	0.14	0.12	0.06	0.06	0.06	0.34	0.36	0.34
20.	115	111	125	130	0.16	0.18	0.18	0.06	0.06	0.04	0.30	0.30	0.30
21.	120	133	133	150	0.16	0.16	0.16	0.06	0.06	0.06	0.30	0.30	0.30
22.	120	116	126	116	0.16	0.18	0.18	0.08	0.08	0.08	0.36	0.36	0.30
23.	120	111	115	107	0.12	0.12	0.12	0.04	0.06	0.04	0.28	0.30	0.28
24.	86	86	103	111	0.14	0.16	0.14	0.08	0.06	0.08	0.40	0.40	0.36
25.	109	133	133	133	0.14	0.16	0.14	0.08	0.08	0.08	0.36	0.30	0.30
26.	150	158	158	158	0.10	0.12	0.10	0.04	0.04	0.04	0.28	0.26	0.24
27.	65	86	73	83	0.18	0.18	0.16	0.06	0.06	0.06	0.40	0.34	0.38
28.	133	133	120	133	0.13	0.13	0.14	0.04	0.04	0.04	0.26	0.30	0.26
29.	120	120	133	109	0.16	0.16	0.16	0.08	0.08	0.06	0.32	0.30	0.30
30.	133	120	150	132	0.14	0.12	0.13	0.04	0.04	0.04	0.30	0.30	0.28
31.	82	100	100	96	0.12	0.14	0.14	0.06	0.04	0.04	0.32	0.32	0.24
32.	77	86	103	79	0.15	0.12	0.11	0.06	0.06	0.06	0.36	0.32	0.32
33.	100	100	130	86	0.18	0.18	0.16	0.08	0.08	0.08	0.36	0.36	0.32
34.	133	150	150	120	0.12	0.14	0.14	0.08	0.06	0.06	0.28	0.24	0.24
35.	120	120	136	120	0.14	0.12	0.14	0.08	0.08	0.08	0.32	0.36	0.36
36.	100	100	100	100	0.16	0.18	0.18	0.06	0.06	0.06	0.34	0.32	0.32
37.	120	120	130	130	0.14	0.12	0.14	0.04	0.04	0.04	0.30	0.32	0.30
38.	100	100	120	120	0.14	0.10	Nodal rhythm	0.06	0.06	0.08	0.28	0.36	0.30
39.	79	79	83	71	0.18	0.14	0.14	0.04	0.06	0.04	0.28	0.28	0.26
40.	120	120	120	107	0.12	0.12	0.11	0.04	0.06	0.06	0.28	0.24	0.26

TABLE IIIA

Case No.		Before intubation	On intubation	On inflation of cuff	Effect on QTc interval
3.	QTc	0.34	0.30	0.32	Nil
	QRS	0.08	0.06	0.06	
		0.26	0.24	0.26	
4.	QTc	0.36	0.38	0.34	Shortened by inflation of cuff
	QRS	0.04	0.04	0.04	
		0.32	0.34	0.30	
6.	QTc	0.42	0.38	0.38	Shortened by intubation and inflation of cuff
	QRS	0.08	0.08	0.08	
		0.34	0.30	0.30	
10.	QTc	0.36	0.32	0.36	Shortened by intubation and prolonged by inflation of cuff
	QRS	0.06	0.06	0.04	
		0.30	0.26	0.32	
11.	QTc	0.28	0.24	0.24	Shortened by intubation and inflation of cuff
	QRS	0.06	0.06	0.06	
		0.22	0.18	0.18	
12.	QTc	0.26	0.34	0.30	Prolonged by intubation and shortened by inflation of cuff
	QRS	0.08	0.08	0.08	
		0.18	0.26	0.22	
16.	QTc	0.24	0.28	0.26	Nil
	QRS	0.06	0.08	0.08	
		0.18	0.20	0.18	
18.	QTc	0.28	0.24	0.24	Nil
	QRS	0.06	0.04	0.04	
		0.22	0.20	0.20	
22.	QTc	0.36	0.36	0.30	Shortened by inflation of cuff
	QRS	0.08	0.08	0.08	
		0.28	0.28	0.22	
28.	QTc	0.26	0.30	0.26	Prolonged by intubation
	QRS	0.04	0.04	0.04	
		0.22	0.26	0.22	
32.	QTc	0.36	0.32	0.32	Shortened by intubation
	QRS	0.06	0.06	0.06	
		0.30	0.26	0.26	
33.	QTc	0.36	0.36	0.32	Shortened by inflation of cuff
	QRS	0.08	0.08	0.08	
		0.28	0.28	0.24	
34.	QTc	0.28	0.24	0.24	Nil
	QRS	0.08	0.06	0.06	
		0.20	0.18	0.18	
35.	QTc	0.32	0.36	0.34	Prolonged by intubation
	QRS	0.08	0.08	0.08	
		0.24	0.28	0.28	
38.	QTc	0.28	0.36	0.30	Prolonged by intubation
	QRS	0.06	0.06	0.08	
		0.22	0.30	0.22	
40.	QTc	0.28	0.24	0.26	Shortened by intubation
	QRS	0.04	0.06	0.06	
		0.24	0.18	0.20	

The QTc intervals (tables III, IIIa) also varied, but these variations were all within normal limits.

The QTc interval was shortened on intubation in 5 cases (nos. 6, 10, 11, 32, 40) and on inflation of the cuff in 6 cases (nos. 4, 6, 11, 12, 22, 33). These changes are most likely due to vagal stimulation.

The QTc interval was prolonged on intubation in 4 cases (nos. 12, 28, 35, 38) and on inflation of the cuff in 1 (no. 10). These changes are possibly due to sympathetic stimulation. All received gallamine and the vagolytic action of this relaxant may result in a relative sympathetic stimulation.

Axis Rotation.

From a perusal of the literature it would appear there are no previous studies of the axis rotation, using the three standard leads, in relation to intubation and inflation of the cuff.

On intubation, 17 cases showed no axis rotation, 18 negative axis rotation, and 5 positive axis rotation. For the 40 cases the average deviation was −0.5 in the scale adopted, which corresponds to about −3°. In 4 cases (nos. 7, 22, 29, 32) the axis rotation produced on intubation appeared to persist during inflation of the cuff (table V).

On inflation of the cuff 18 of the remaining 36 cases showed no axis rotation, 13 showed positive rotations and 5 showed negative rotations.

Again the average rotation was approximately 0.5 on the scale adopted which corresponds to +3°.

In 4 cases (nos. 2, 3, 25, 36) there appeared to be a delayed effect produced by intubation, and in 9 cases (nos. 4, 11, 12, 16, 24, 27, 28, 30, 35) the rotation produced by inflation of the cuff persisted and in some cases was larger on the first reading after inflation of the cuff.

One case (no. 39) showed an anomalous result between the reading on inflation of the cuff and the first reading after inflation of the cuff.

Six cases (nos. 8, 14, 20, 21, 37, 40) showed no axis rotation effects during the period investigated.

Single lead changes may give an erroneous impression of certain changes which the three leads considered together clarify and show to be only changes in electrical axis.

Johnstone (1956) has noted axis changes due to other causes such as certain postures, thoracotomy, complete curarization and controlled ventilation with deep inflation.

The mechanism of the axis rotation is not clear but it is not related to changes in pulse rate, blood pressure or drugs. Amongst the possibilities are the effect of the metal stylet acting as an induced electrical dipole; a study of the relation between the axis rotation and the initial axis inclination showed that any such effect must only be small and was certainly masked in this investigation by other effects.

No correlation was found between the pressor response to intubation and the axis rotation.

Neither was any correlation found between axis rotation and the administration of hexamethonium or chlorpromazine.

As the relaxant used in the majority of cases was gallamine the number of cases receiving other relaxants was small; this means it would only be possible to detect gross changes in the axis rotation response to the relaxant used. No such change was found.

QRS Electrical Vector.

Instead of studying the QRS complex as seen in the individual leads the true QRS vector has been considered. In only 8 cases were significant changes found and 6 of these were on the first reading after the inflation of the cuff and 2 on

TABLE IV

*Changes in QRS Electric Vector.**

(Combination of all 3 leads).

Case No.	On intubation	On inflation of cuff	First reading after inflation of cuff
10.	No change	No change	+5 mm
15.	,,	− 5 mm	Change disappeared
18.	,,	No change	+5 mm
21.	,,	,,	−3 mm
27.	,,	,,	+5 mm
28.	,,	−4.5 mm	Change disappeared
32.	,,	No change	+3.5 mm
39.	,,	,,	−3.0 mm

* Significance level = 3 mm.
For method of calculation see appendix.
Case No. 15 is illustrated in figure 2, and Case No. 21 in figure 4.

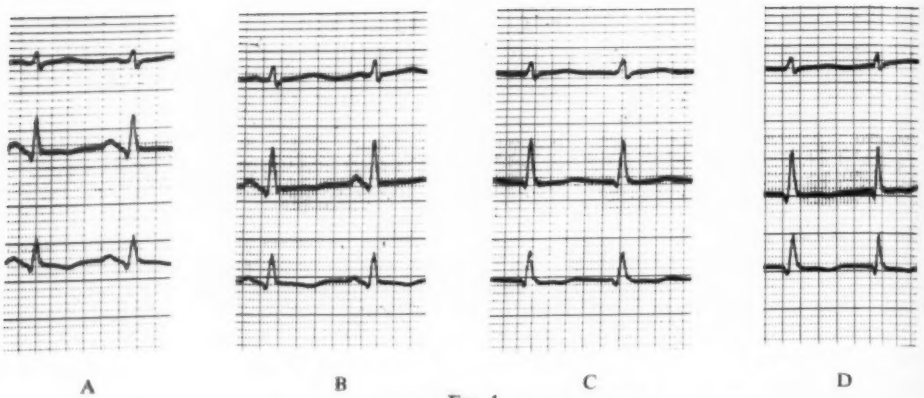

FIG. 1

Case No. 38. Nodal rhythm on inflation of cuff.

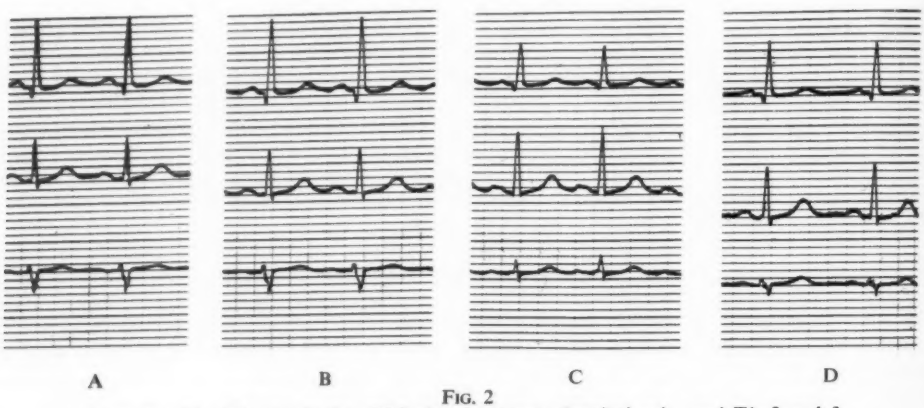

FIG. 2

Case No. 15. Changes in P1, QRS electric vector, electrical axis, and T1, 2 and 3, on inflation of cuff.

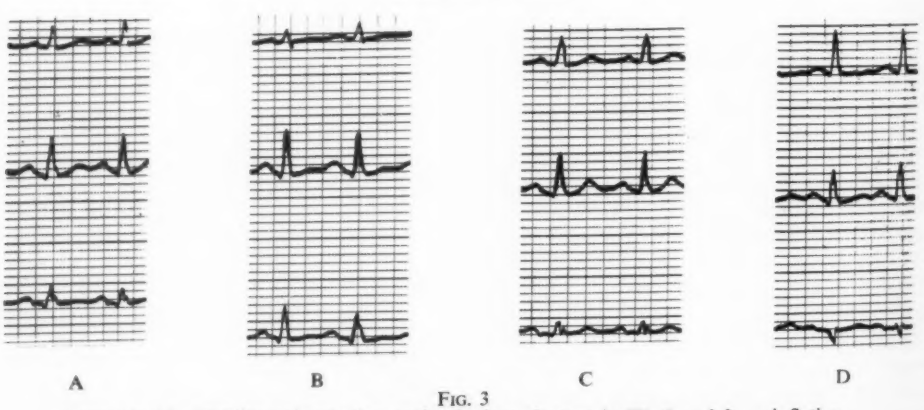

FIG. 3

Case No. 16. Positive axis rotation on intubation; changes in T1, 2 and 3 on inflation of cuff, and negative axis rotation on first reading after inflation of cuff.

A = Before intubation.
B = On intubation.
C = On inflation of cuff.
D = First reading after inflation of cuff.

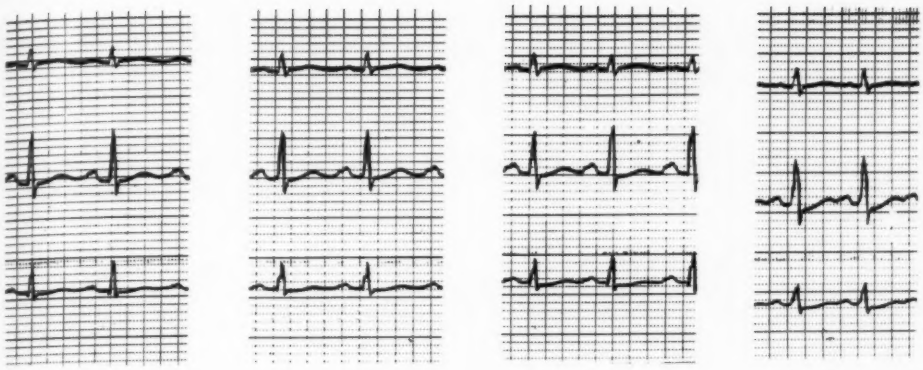

FIG. 4

Case No. 21. Changes in QRS electric vector, and ST2 depression on first reading after inflation of cuff.

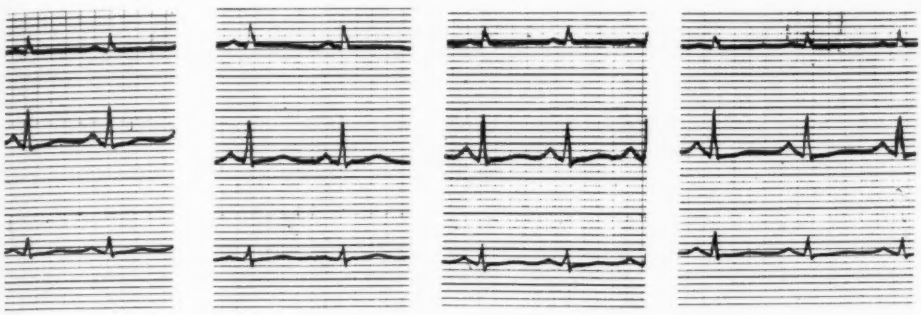

FIG. 5

Case No. 36. Changes in P1 and electrical axis on intubation; change in electrical axis on first reading after inflation of cuff.

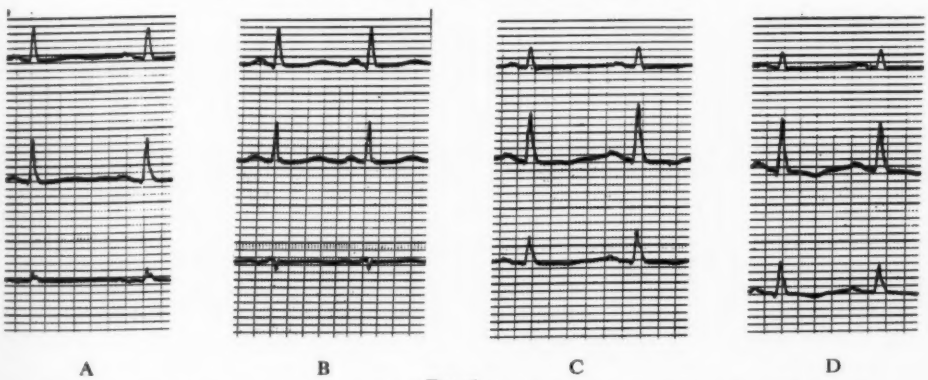

FIG. 6

Case No. 24. Axis rotation on intubation, inflation of cuff and first reading after inflation of cuff; T1 and 2 changes on inflation of cuff; T2 and 3 changes on first reading after inflation of cuff.

A = Before intubation.
B = On intubation.
C = On inflation of cuff.
D = First reading after inflation of cuff.

inflation of the cuff (table IV). The latter 2 cases were associated with marked axis rotation whereas no marked rotation occurred in the other 6 cases. Clearly, observations in a single lead will cause apparent changes in QRS voltage when axis rotation occurs.

In fact it appears that very little change in the magnitude of the QRS vector occurs on either intubation or inflation of the cuff; it is possible that the 6 cases where changes occurred on the first reading after inflation of the cuff were due to other causes.

TABLE V

*Changes in Electrical Axis.**

Key. All axis changes are related to electrical axis immediately prior to intubation.

0°– 5° = 0	16°–20° = 3
6°–10° = 1	21°–25° = 4
11°–15° = 2	26°–30° = 5

Case No.	Electrical axis prior to intubation	Changes in axis on intubation	Changes in axis on inflation of the cuff	Changes in axis, first reading after inflation of the cuff
1.	46°	−1	0	–
2.	−10°	0	0	+1
3.	84°	−4	0	−1
4.	48°	−1	+1	+1
5.	34°	−1	0	–
6.	20°	+2	0	0
7.	− 1°	−1	−1	0
8.	57°	0	0	–
9.	55°	0	+2	0
10.	96°	−1	0	0
11.	36°	0	+4	3
12.	6°	0	−1	−1
13.	27°	0	+3	–
14.	13°	0	0	–
15.	17°	0	+3	–
16.	54°	+4	−1	−5
17.	30°	+2	+1	–
18.	62°	0	−1	–
19.	45°	0	+1	0
20.	42°	0	0	0
21.	70°	0	0	0
22.	54°	−5	−2	−1
23.	44°	−3	0	0
24.	42°	−3	+4	+5
25.	−26°	−1	0	+4
26.	26°	−2	0	0
27.	78°	−1	+1	+1
28.	28°	−1	+4	+3
29.	65°	−1	−1	0
30.	55°	0	+1	+4
31.	72°	0	+2	0
32.	41°	−3	−4	0
33.	63°	−1	0	0
34.	18°	0	+2	–
35.	25°	+1	−4	−2
36.	59°	−2	0	+2
37.	38°	0	0	–
38.	76°	−1	0	–
39.	−21°	+2	−1	+1
40.	76°	0	0	–

* For method of calculating electric axis see appendix.

Figures 2 and 3 illustrate marked changes on inflation of the cuff (No. 15) and intubation (No. 16) respectively.

ST Segment Changes.

These occurred in only 1 case (no. 21) during the first reading after inflation of the cuff when the ST depression was increased (table VI).

T Wave Changes.

In 9 cases the T wave changes occurred on inflation of the cuff whereas only in 1 case (no. 8) was a T wave change found on intubation. In this T2 and 3 were depressed by 2.0 mm. The T2 depression disappeared on inflation of the cuff and the T3 depression by the first reading after inflation of the cuff (table VII).

CONCLUSIONS

In the 40 cases studied no serious arrhythmia and no cardiac arrest was encountered. Care was taken to avoid hypoxia and hypercarbia and cyclopropane was not used. One case of nodal rhythm occurred on inflation of the cuff (no. 38), but on the other hand in 1 case (no. 29) ventricular extrasystoles which were present prior to intubation disappeared after intubation.

Rotation of the electrical axis occurred in the majority of cases on intubation and inflation of the cuff. The use of the three standard leads was necessary to detect these changes. On intubation the average rotation was $-3°$ and on inflation of the cuff $+3°$.

The true QRS vector did not appear to show significant changes during intubation and inflation of the cuff, but the QRS voltage measured in a single lead showed changes due to axis rotation.

There was no significant correlation between the e.c.g. changes reported and those cases receiving hexamethonium or chlorpromazine.

The administration of hexamethonium eliminated the pressor response to intubation.

TABLE VI
ST Segment changes

Case No.	On intubation	On inflation of cuff	First reading after inflation of cuff
21.	No change	No change	ST2 depression increased by 1.0 mm

This case is illustrated in figure 4.

TABLE VII
T Wave Changes

Case No.	On intubation	On inflation of cuff	First reading after inflation of cuff
4.	No change	T2 raised by 1.0 mm	Change disappeared
5.	,,	T2 depressed by 1.0 mm	,, ,,
6.	,,	T1 raised by 1.0 mm	,, ,,
8.	T2 & 3 depressed by 2.0 mm.	T3 depressed by 2.0 mm	,, ,,
10.	No change	T2 & 3 depressed by 1.0 mm	,, ,,
15.	,,	T1 depressed by 1.0 mm T2 & 3 raised by 1.0 mm	,, ,,
16.	,,	T1 & 3 raised by 1.0 mm T2 raised by 2.0 mm	,, ,,
24.	,,	T1 depressed by 1.0 mm T2 changed from +1.0 mm to −0.5 mm	T2 became −2.0 mm T3 depressed by 1.0 mm
39.	,,	T3 raised by 1.0 mm	Change disappeared

Case No. 15 is illustrated in figure 2, and Case No. 24 in figure 6.

The use of all three standard leads simultaneously is essential for a comprehensive interpretation of the e.c.g. changes which occur.

SUMMARY

The e.c.g. changes associated with intubation and inflation of the cuff using three standard leads have been studied in 40 cases.

The two most significant changes observed were, firstly, changes in the direction of the electrical axis which occurred in most cases and, secondly, the absence of a pressor response to intubation in those cases which received hexamethonium.

Changes in the P and T waves and in the PQ, QRS and QTc intervals are reported.

In one case a nodal rhythm occurred on inflation of the cuff, in a second case an ST depression increased after inflation and in a third case ventricular extrasystoles disappeared on intubation.

APPENDIX

The electrical axis direction of the QRS complex was calculated by measuring the magnitude of the height of the R and S peaks in leads I and III.

The lead I electric vector, l_1, is the algebraic sum of the heights of the R and S peaks and similarly l_3 is the electric vector for lead III.

Then it is easy to show that

$$\tan V = \frac{\frac{l_3}{l_1} + \frac{1}{2}}{\text{Sin } 60^\circ}$$

and $E = l_1 \text{ Sec } V$ where V is the direction of the electric axis and E is the magnitude of the electric vector for the QRS complex.

E and V were calculated by the use of these formulae and form the basis of tables IV and V.

ACKNOWLEDGMENTS

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ANAESTHESIA FOR PROSTATECTOMY

BY

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INTRODUCTION

IT is likely that in the future prostatic surgery will increase, owing to the slow ageing of the population. Patients with prostatic obstruction present many problems to the surgeon and anaesthetist. These fall into two broad groups—complications due to the disease itself, such as infection and impaired renal function, and those general complications seen in any older age group of patients, the commonest in this country being chronic bronchitis and emphysema, hypertension, hypertensive heart disease, and coronary and cerebral arteriosclerosis.

The anaesthetic requirements for such a group of patients, few of whom do not have associated cardiovascular and respiratory disease, are exacting, and the ideal anaesthetic technique that will produce light anaesthesia, complete relaxation, and a dry operation field without hypotension has yet to be found. Light anaesthesia is very important: these patients should be able to drink within an hour of operation to keep up their fluid intake, and be able to cough and move about to diminish the risk of pulmonary embolism and chest complications, to which they are particularly prone. Complete relaxation is an essential for the Millin retropubic operation where access in obese patients may present technical difficulties. Excess bleeding at operation is dangerous, for these patients stand blood loss poorly, and it prolongs the operating time. It is the opinion of the authors that epidural anaesthesia approaches this ideal and represents the best compromise between the various anaesthetic techniques available at the present time. Before passing to a detailed consideration of epidural anaesthesia in prostatic surgery it is useful to consider the advantages and disadvantages of other methods.

METHODS OF ANAESTHESIA

General Anaesthesia.

This involves in modern anaesthetic practice a thiopentone–nitrous oxide–relaxant sequence with controlled respiration. The principal disadvantage of general anaesthesia is that it does nothing to minimize bleeding at operation, the patient nearly always requiring blood transfusion as a result. The swing towards hypotensive techniques in recent times has probably been a direct result of the uncontrollable ooze of present-day nitrous oxide–oxygen–relaxant techniques (Gray, 1957). Gillies (1952) himself has acknowledged that the extensive use of cyclopropane in Edinburgh had undoubtedly contributed to the ready appreciation there of the dry surgical field produced by total spinal block.

There has from time to time been a good deal of discussion as to the correct anaesthetic management of patients with chronic bronchitis and emphysema—a very commonly associated disease in the prostatic patient. The physiological basis of positive pressure therapy in emphysema is well known and has been described in detail by American workers (Barach, 1948; Segal and Dulfano, 1953). It might be thought, therefore, that controlled respiration would be the most physiological method of dealing with the chronic bronchitic and emphysematous subject undergoing a surgical operation. Such methods of intermittent or continuous positive pressure therapy as described by Barach are employed with conscious patients whose full co-operation can be obtained. Conditions are very different in a fully curarized patient undergoing a surgical operation where complicating factors such as blood loss enter the picture. Controlled respiration reverses the normal pressure conditions in the thorax and the

venous return is reduced during positive pressure inspiration. To overcome this a rise in venous pressure occurs, brought about by peripheral vasoconstriction—a compensatory mechanism to keep the cardiac output from falling. This rise in venous pressure during controlled respiration results in increased capillary and venous haemorrhage and may result also in degrees of shock out of proportion to the blood loss. The sort of difficulty which can be experienced with the chronic bronchitic on controlled respiration is well described by Johnstone (1956) recording the case of a patient aged 62 for suprapubic prostatectomy with chronic diffuse obstructive emphysema. Anaesthesia was induced with thiopentone and suxamethonium followed by orotrachael intubation and inflation with 50 per cent nitrous oxide and oxygen. After a few inflations the diaphragm was displaced deeply in the abdominal cavity and showed no sign of returning spontaneously. The patient was cyanotic, with a barely perceptible pulse. Manual compression of the upper abdomen and chest resulted in a prompt return of the pulse and colour. Spontaneous respiration returned, and after a further dose of suxamethonium and inflation the same thing happened. The operation was abandoned, and a successful suprapubic prostatectomy was done under spinal analgesia at a later date. Many other anaesthetists have recorded how the high inflation pressures required in patients with chronic bronchitis and emphysema may cause collapse of the cardiovascular system.

Auld (1956) records a case of gaseous imbalance produced by controlled respiration in an emphysematous subject. At the end of operation anoxia had to be allowed to develop before respiration would start, in spite of reversal of curarization.

General Anaesthesia plus Hypotension.

Considerable improvement can be made in the operating field provided by general anaesthesia by the use of hypotensive techniques. Much evidence is now available to show that hypotensive techniques are potentially dangerous and should never be used in the absence of a specific and urgent indication or for the convenience of surgery. The use of hypotensive techniques in prostatic patients, who are very likely to have cerebral and coronary atherosclerosis, would seem to be quite unjustified.

Spinal Analgesia.

This undoubtedly overcomes many of the difficulties associated with general anaesthesia. Relaxation is perfect and haemorrhage considerably reduced. The immediate disadvantage is that the patient has to be nursed flat for 24 hours to diminish the risk of spinal headache. This is unsatisfactory in patients with chronic respiratory disease, and may be ineffective in a patient with a cough.

A great disadvantage of spinal analgesia appears to be detrussor weakness present for some hours, with absence of "vis a tergo" to keep the bladder empty and so minimize the tendency to clot formation (Magill, 1947).

Far more serious is the risk of permanent neurological damage. If spinal analgesia carried no risk of permanent neurological damage it would approach the ideal technique, as the production of spinal analgesia is relatively simple.

Mention must be made of the so-called "haemostatic spinal", the theory of this being that in a saddle block spinal paralysis of the sacral parasympathetic results in vasoconstriction in the prostatic bed because of the unopposed action of the lumbar sympathetic supply. Dale (1953) and Swerdlow (1953) have reported excellent results from a combination of low spinal analgesia with an abdominal field block. The method gives good results from the point of view of bleeding but requires several injections and the patient is subjected to the risks of spinal analgesia. If the field block is omitted because the patient prefers to be asleep, and general anaesthesia is used in its place, the same arguments against a combination of spinal and general anaesthesia apply.

Epidural Analgesia.

The principal advantage of epidural analgesia is that whilst the operating conditions are equal to that of the spinal, there is no spinal headache, and the risk of permanent neurological damage is probably much reduced. No reports of permanent neurological damage following epidural analgesia have yet appeared in the literature: three such cases, however, are known (Dawkins, 1957). The blood pressure is readily under the control of the anaesthetist and can be kept at safe levels and yet provide for operating conditions

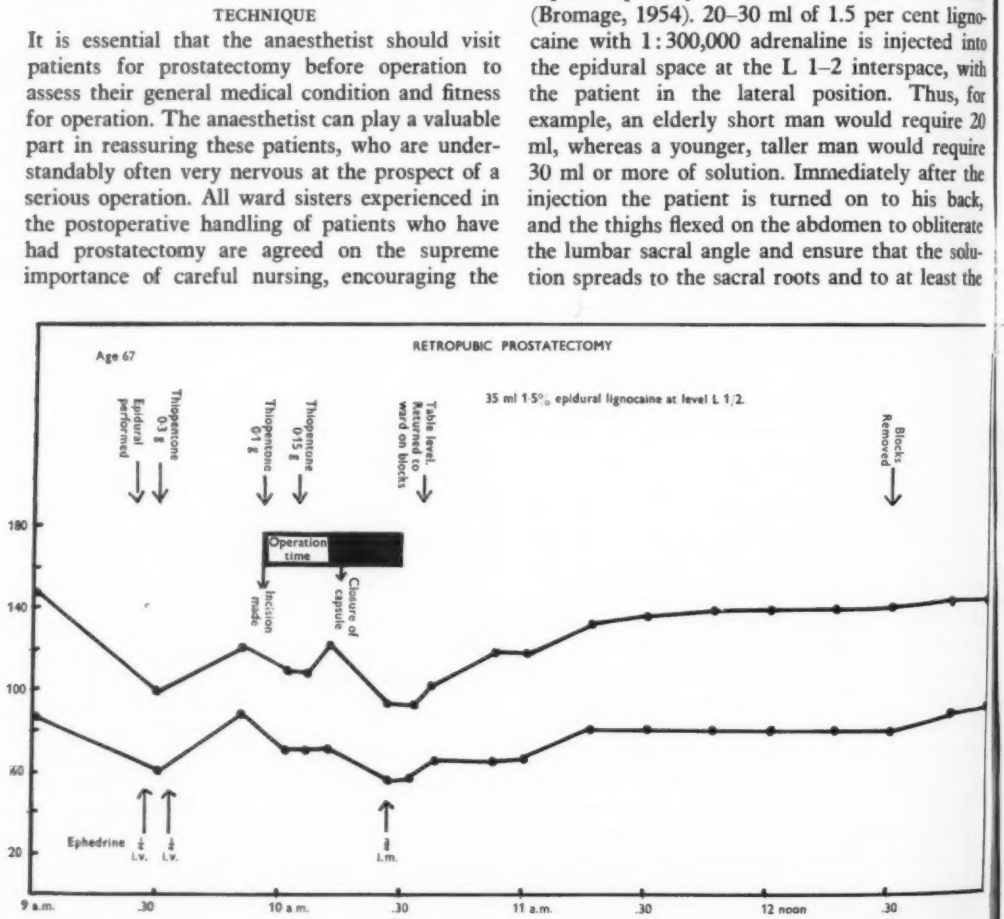
superior from the point of view of bleeding to those obtained with general anaesthesia plus relaxants. Postoperatively the patient can be sat up and encouraged to cough and move around as soon as the blood pressure has remained stable for two hours. The time before analgesics are required postoperatively is much greater after epidural analgesia than after general anaesthesia, and many patients require no postoperative analgesics at all (Dawkins, 1954). The difficulties of producing epidural analgesia have probably been over stressed: the technique can easily be learned by anyone who has the interest and patience to do so.

TECHNIQUE

It is essential that the anaesthetist should visit patients for prostatectomy before operation to assess their general medical condition and fitness for operation. The anaesthetist can play a valuable part in reassuring these patients, who are understandably often very nervous at the prospect of a serious operation. All ward sisters experienced in the postoperative handling of patients who have had prostatectomy are agreed on the supreme importance of careful nursing, encouraging the patient to drink, move about, and to cough. The anaesthetist in these circumstances can be of great assistance to their efforts.

Retropubic Prostatectomy.

The premedication is morphia 10 mg, atropine 0.65 mg for patients over 60 years of age, and papaveretum 20 mg, scopolamine 0.45 mg for younger patients. For the retropubic operation a relatively large volume of solution is required as the solution can escape easily through the large anterior sacral foramina. The volume of solution is chosen according to the height of the patient and the expected patency of the intervertebral foramina (Bromage, 1954). 20–30 ml of 1.5 per cent lignocaine with 1:300,000 adrenaline is injected into the epidural space at the L 1–2 interspace, with the patient in the lateral position. Thus, for example, an elderly short man would require 20 ml, whereas a younger, taller man would require 30 ml or more of solution. Immediately after the injection the patient is turned on to his back, and the thighs flexed on the abdomen to obliterate the lumbar sacral angle and ensure that the solution spreads to the sacral roots and to at least the



10th thoracic segment. Ephedrine 15 mg is given intravenously and 15 mg intramuscularly to forestall any fall of blood pressure. After five minutes the legs are lowered and the incision infiltrated with 1:150,000 adrenaline in saline as a purely haemostatic measure. Because of the uncomfortable Trendelenburg position during operation the patient is given a sleep dose of thiopentone. Supplemental doses of thiopentone may be needed to maintain sleep during operation; the average total amount is about 250–400 mg of a 5 per cent solution. Further doses of vasopressor may be required during the operation of the order of 7.5–15 mg. A chart showing the blood pressure changes during a typical retropubic prostatectomy under epidural analgesia is shown. It is most important that the blood pressure should be within 80 per cent of normal before the capsule is sutured: in this way the risk of reactionary haemorrhage is eliminated.

At the conclusion of the operation the patient is usually awake and talking and can return to the ward and be encouraged to drink. He is nursed flat until the blood pressure has remained at at least 100 mm/Hg for 2 hours. Usually no vasopressor is required postoperatively, but it is an important part of the technique that the anaesthetist ensures that the blood pressure is kept to near normal levels during the immediate postoperative period when the epidural is wearing off.

Transurethral Prostatectomy.

For these patients 15–20 ml of 1.5 per cent lignocaine is injected at L 3–4 interspace with the patient sitting up. Vasopressors are given if necessary, as described for the retropubic operation, but normally there is little or no fall in blood pressure with such a low block. No thiopentone is required, as the Trendelenburg position is not used. Patients tend to become drowsy after epidural lignocaine and often sleep during operation. Postoperatively the majority have no memory of being operated on. Back in the ward they can be roused and encouraged to drink and move their limbs at regular intervals.

RESULTS

Retropubic Prostatectomies.

Seventy-one cases had epidural anaesthesia for retropubic prostatectomy (table I).

There were five deaths within one month of operation, a mortality of approximately 7 per cent. Two were on the day following operation: one suddenly, of coronary thrombosis

TABLE I

Age group	No. of cases	Fit patients for age	Hypertension of B.P. more than 180/100 mm Hg	Other C.V.S. complications	Respiratory complications	Miscellaneous
40 to 50	2	1	1	–	–	–
50 to 60	8	7	1	–	–	–
60 to 70	23	8	5	–	8	1 Ca. rectum. 1 severe Parkinson's.
70 to 80	28	12	8	1 Stokes Adams attacks.	5	1 Paget's. 2 Parkinson's (1 severe). 1 severe arthritis.
80 to 90	9	7	–	1 coronary thrombosis (1 year ago). 1 gross arteriosclerosis with amputation right leg.	–	–
90 to 100	1	1	–	–	–	–

(aged 65); the other, of pulmonary embolism from the calf veins, was aged 74, with blood pressure 240/130 mm Hg, and had emphysema with poor chest expansion. One died on the third postoperative day following a right cerebral thrombosis and bronchopneumonia. He was 69 years old and his pre-operative blood pressure was 210/110 mm Hg. The fourth, aged 80, died of bronchopneumonia on the eighth postoperative day. The fifth died of bronchopneumonia on the thirteenth postoperative day.

Of the remaining 66 cases, one patient, aged 72, with severe rheumatoid arthritis and hypertension developed a cerebral thrombosis the following day but made a complete recovery. Another, aged 73 but fairly fit before operation, had a left hemiplegia the following day and also recovered completely. Only one had a reactionary haemorrhage, subsequently shown to be due to a disorder of the clotting mechanism. This patient, who was aged 73, had a carcinoma of the prostate. There were four secondary haemorrhages on or after the seventh postoperative day. No patient received a blood transfusion during operation and only three during the postoperative period: two of these were for secondary haemorrhage.

Transurethral Prostatectomies.

Forty-three cases had epidural anaesthesia for transurethral prostatectomy. Of these, 24 were poor risk patients due to various causes—hypertension, cardiac failure, chronic bronchitis, etc. Three patients died, a mortality of approximately 7 per cent. One aged 59, who had emphysema and chronic bronchitis, and an electrocardiogram showing ischaemic changes pre-operatively, died of coronary insufficiency during the operation. The second died on the eighth postoperative day, but at operation was already a dying man due to carcinoma of the prostate with secondaries in the brain. The third, aged 75, died on the twenty-second postoperative day. Death was due to carcinoma of prostate, acute bilateral pyelonephritis and acute bronchitis. One patient had a minor secondary haemorrhage but did not require transfusion. There was no other morbidity.

The overall mortality for the two groups of cases was 7 per cent.

The suitability of epidural anaesthesia for prostatic surgery must be judged by its effects on both operation and postoperative management, since operative ease cannot legitimately be purchased at the price of postoperative difficulty. During the operation itself the absence of haemorrhage is impressive. Infiltration of the abdominal wall contributes to this, eliminating the obscuring effects of trivial bleeding so that the anatomy of the retropubic space is clear and precise and the uncongested veins in front of the capsule are easily caught and diathermied. Major vessels in the divided capsule bleed vigorously and need to be diathermied, but the usual obscuring ooze is absent and the bulging prostatic adenoma is clearly seen. Enucleation is not accompanied by major haemorrhage, so that after removal of the adenoma individual bleeding vessels inside the capsule can be readily and thoroughly controlled. It is not unusual for the sucker bottle to remain uncontaminated throughout. Good vision allows good capsular closure and the operation is usually completed in between 20 and 30 minutes. Major vessels bleed freely under epidural analgesia, and are promptly controlled, so that there is not an increase in the incidence of haematoma, but the general uncontrollable and obscuring ooze which commonly robs surgery of speed and precision is completely prevented.

In this series patients undergoing prostatectomy usually return to the ward between 10 and 11.30 a.m. By early afternoon they are usually sitting up and drinking well and by the evening reading their newspapers and demanding supper. As a result good urinary drainage is established early, with consequent reduction in the risk of blocked catheters. Milan (1947) reported one clot retention and two wound haemorrhages requiring surgical interference in 375 cases. This record can seldom have been equalled, but in the present series reactionary haemorrhage with clot retention only occurred once, and this patient was subsequently found on investigation to have a disorder of the clotting mechanism. Magill (1947) has put forward the view that spinal anaesthesia weakens the bladder contractibility and favours clot retention, and it might be argued that the same would apply to extradural anaesthesia: however,

the occurrence of only one reactionary haemorrhage in the series shows this not to be so.

Blood transfusion is not free from hazard in any patient, least of all in old men, but Johnson (1953) found it necessary in 6 per cent of a large series of prostatectomies under general anaesthesia in spite of meticulous anaesthetic technique. In many centres it is now routine practice to transfuse a pint of blood at operation in patients under general anaesthesia. The fact that in no case was blood transfusion required at operation in the present series is felt to be a distinct advantage of the technique.

Secondary haemorrhage between 6 and 16 days after operation is of course a complication of all prostatic surgery, and not related to anaesthesia. Many cases have a urine which is barely pink 48 hours after operation while others take a further 48 hours to clear completely, but seldom longer. Millin's (1947) " vin rosé " is often in evidence, but " sherry " is seldom seen. Certainly there has never been evidence of prolongation of the period of postoperative bleeding after retropubic or transurethral prostatectomy to mar the advantages of epidural analgesia.

DISCUSSION

A recent leading article in the *Lancet* (1956) has drawn attention to the difference in the results of prostatectomies performed in two centres—Hospital A and Hospital B. This series of cases is reported from a nonteaching hospital, which must be regarded as Hospital B. It is in Hospital B that the worst risk cases are likely to be encountered. Hospital B very often has a liaison with a chronic sick institution and may have a large waiting list, so that a high proportion of enlarged prostates come in as emergencies with acute retention—approximately 60 per cent in this series. The series is admittedly small, but an overall mortality of 7 per cent compares favourably with mortality published from Hospital A. Riches (1949) quoted a mortality of 6.2 per cent in 321 cases of retropubic prostatectomy. Jacobs (1951), reporting 500 cases of retropubic prostatectomy from the Urological Department, Glasgow Royal Infirmary, quotes an overall mortality of 6 per cent. Bryne (1952) has reported a series of 347 private cases of which 202 (58 per cent) had a transurethral resection with a mortality of 5.4 per cent and 62 one-stage suprapubic prostatectomies (presumably transvesical) with a mortality of 6.4 per cent. Caine (1954) gives a mortality of 6.8 per cent for the Millin retropubic operation and 7.1 per cent for transurethral resection, from the Institute of Urology. Dawson-Edwards (1956), surveying 810 cases of prostatectomy from the Urological Unit of the Queen Elizabeth Hospital, Birmingham, gives a mortality of 4.6 per cent (teaching hospital mortality). It is of interest to note that the commonest cause of death in this series was pulmonary embolism.

Bedford (1955), in a recent paper, analyzes in great detail the adverse cerebral effects of anaesthesia in old people. During a five-year period, of 4,250 patients seen in the Oxford Geriatric Unit at Cowley Road Hospital, 251 (6 per cent) underwent a surgical operation under general anaesthesia, and of these 18 (7 per cent) could be shown to have suffered some degree of cerebral damage. He shows clearly in the case records what a vital part falls in blood pressure play in the development of cerebral damage after operation. We have described the control of the blood pressure during prostatectomy under epidural analgesia and postoperatively, and we consider that the excellent operating conditions, complete relaxation with spontaneous respiration, and minimal blood loss, at normal levels of blood pressure, constitute its principal advantages. Other factors in the development of cerebral damage, such as deep narcosis and heavy postoperative sedation, are eliminated by the use of epidural analgesia.

It is clear that no method of anaesthesia for prostatic surgery is the complete answer to the problem. The writers are of the opinion, both on theoretical grounds and from these results, that epidural analgesia is the best method available at the present time. In searching for the ideal anaesthetic the anaesthetist is always strongly influenced by what is the safest from the patient's point of view. However, such an anaesthetic may provide poor or impossible operating conditions, and it must not be forgotten that the surgeon has his problems too, and the better the operating conditions the quicker and better a technical operation he will be able to do. The result, there-

fore, is bound to be a compromise. It is well recognized that epidural analgesia carries with it a slight but definite morbidity, though this can be reduced to negligible proportions by careful technique, and this, of course, applies to general anaesthetics as well. The following figures are quoted for the incidence of a total spinal analgesia for epidural injections performed in the lumbar area:

Moore (1953)	0 in 1,700 cases	
Bonica (1955)	1 in 2,290 cases	0.04 per cent
Selva de Assis (1953)	2 in 1,000 cases	0.2 per cent
Bromage (1954)	1 in 1,000 cases	0.1 per cent

The total spinal should not be regarded as a catastrophe, but as a treatable occurrence. Provided immediate measures are applied to keep the blood pressure up and the lungs ventilated until full spontaneous respiration returns, no harm will ensue.

SUMMARY

114 prostatectomies performed under epidural anaesthesia at a nonteaching hospital are reported, and the mortality and morbidity analyzed.

The overall mortality was 7 per cent. No case required transfusion at operation. There was one case of reactionary haemorrhage which required transfusion in the postoperative period, subsequently shown to be due to a disorder of the clotting mechanism.

The advantages and disadvantages of the various methods of anaesthesia for prostatectomy are discussed.

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A SUCTION CATHETER HOLDER

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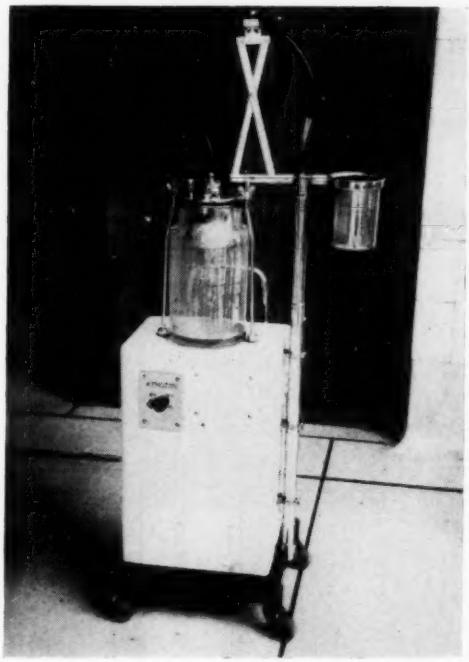
THIS attachment for an "Atmozon" suction machine consists essentially of a metal tube, about 2½ feet long and of about an inch outside diameter, which can be clipped to the side of the machine. The tube is in three sections which are a tight push-fit, the one into the other. The sections can thus be easily cleaned and sterilized, even in a small sterilizer. The lower section has a liquid-tight cap so that this section can be filled with a bland antiseptic solution. The upper section has a fixed collar about ¾ inch from the top to support a horizontal detachable bar. One arm of this bar carries a vertical support with a "Terry" type clip and flanges at its top (which is at about the level of the patient's lips as he lies on the operating table) to carry the loops of pressure tubing. Under the vertical support attached to the horizontal arm, is a small rotating screw collar which fits on to one of the suction bottle supports, hence further anchoring the attachment to the machine but still allowing of easy detachment of the tube for cleaning. The other arm of the bar carries a ring support for a gallipot, or metal container to hold bland liquid which can be used to test the suction and to clear the catheter of viscid secretions. The attachment has been made of brass and then chromium plated throughout.



The manufacturers of the above are Messrs. Silten Ltd., Silten House, Hatfield, Herts.

Brit. J. Anaesth. (1957), **29**, 384

EXPENDABLE PLASTIC TUBES FOR USE WITH CATHETER HOLDER

BY

D. G. HUNTLY

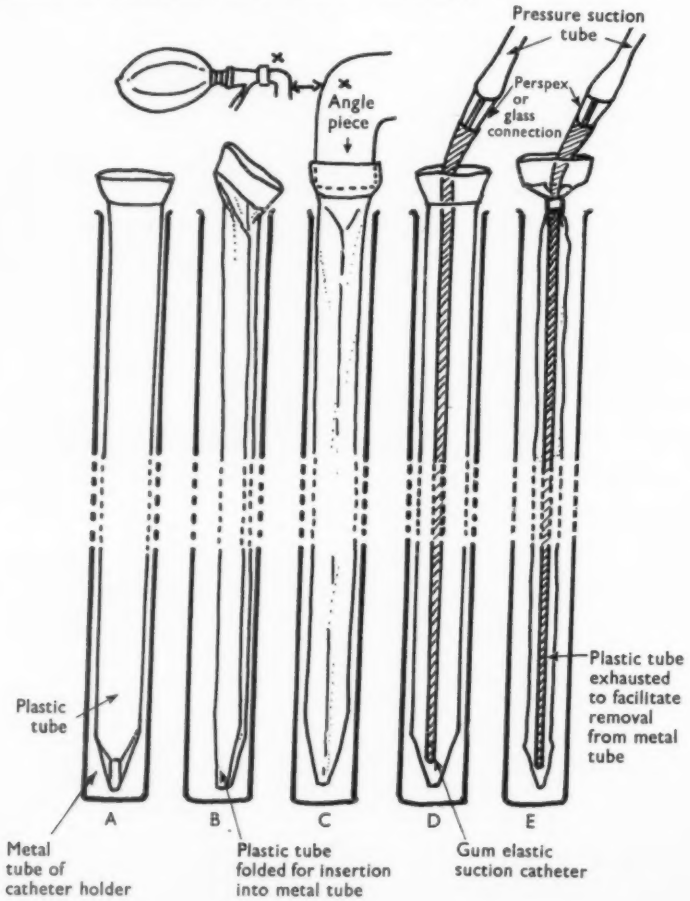
Clayton Hospital, Wakefield, Yorks

FOR cleanliness and ease of maintenance a plastic lining tube can be used with a suction catheter holder. This is expendable and can be destroyed at the end of each case, thus obviating the necessity of dismantling and cleaning the metal tube between cases.

The plastic tube is folded on itself longitudinally for ready insertion into the metal tube. The plastic tube is then inflated to fill the metal tube. This can conveniently be done from the anaesthetic machine by means of rebreathing bag, Waters T-piece and angle piece. It is then ready for use.

At the end of the case the plastic tube is constricted at its neck, round the gum elastic catheter. The suction is switched on and the plastic tube is thus exhausted, shrinks from the walls of the metal tube, and can be easily withdrawn.

The plastic tube and its contained catheter (and any septic material) are then removed from the operating theatre—the plastic tube for destroying—the catheter for cleaning and re-sterilizing.



Brit. J. Anaesth. (1957), **29**, 385

PROVISION OF WATER FOR SUCTION

BY

HUGH I. O. ARMSTRONG

West Fife Hospitals Group

THE importance of easily available and maintained suction in anaesthesia is unquestioned.

How often and quickly does the end piece and tubing become clogged with debris, blood clot, etc.?

At this point the anaesthetist requires a bowl of water to clear the tubing and if he has not got it immediately available precious seconds may be lost.

The photograph demonstrates how the clearing water may be carried on the usual B.O.C. cylinder carrier without any adjustments or metal work. All that is required is an unused chromium plated water bath for the ether bottle vaporizer from an old Boyle's Machine and the ether bottle itself. The water bath hooks on to the screw as shown, and by tightening the nut moderately the whole can be made rigid and the entire apparatus wheeled to wherever it is required with the clearing water, self contained.

SENGSTAKEN TUBE TO PREVENT ASPIRATION

Sir,—The necessity for prevention of aspiration of gastric contents into the airways during anaesthesia for operations for ileus or intestinal obstruction is emphasized frequently, but seemingly it is still a problem. The following method which has proven efficient in practice is suggested.

A special tube, described by Sengstaken and Blakemore (1950), which when described was meant for control of oesophageal haemorrhage by compression, is used, but here with another purpose, namely, to provide oesophageal occlusion.

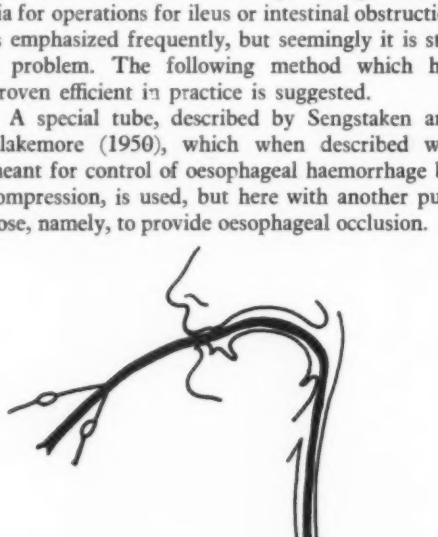


FIG. 1

The tube used is about 40 inches (101.6 cm) long and has two inflatable cuffs. The lower part and the lower cuff are coated with a thin layer of lubricating jelly and the tube is introduced through the nose of the awake patient, if desired after slightly spraying with a topical anaesthetic through the nostrils. When the tube is passed to the 50 cm mark, the lower cuff is inflated with 40–60 ml of air and the tube withdrawn until the impact of the balloon against the cardia is felt. The proximal cuff, which is now in the lower part of the oesophagus, is inflated using about 150–200 ml of air (about 20 mm Hg pressure in the cuff system). The tube is fixed to the nose by adhesive tape. Gastric contents cannot now be regurgitated into the pharynx and therefore the danger of aspiration is removed (fig. 1).

After the anaesthetic, when the swallowing and coughing reflexes have returned, suction is applied to the tube before and during its removal.

The advantage of using this tube instead of merely an oesophageal balloon for this purpose is that proper positioning and its safe fixation ensures that there is no danger of the balloon sliding up into the pharynx or down into the stomach. The lower inflated cuff by itself helps to block the passage upwards.

ARNE RUBEN
Lasarettet, Köping, Sweden

REFERENCE

Sengstaken, R. W., and Blakemore, A. H. (1950). *Ann. Surg.*, **131**, 781.

A CASE OF RESPIRATORY FAILURE

Sir,—The following case report may be of some interest as an illustration of one type of respiratory failure.

The patient was a woman aged 40 who was admitted one morning to a medical ward with severe stridor. She had had a thyroidectomy six years previously, and had complained of occasional stridor since that time. The stridor increased after admission, and at midday I was asked to see her. On arriving in the ward, I found the patient struggling for breath and very cyanosed, her pulse was rapid and feeble and she was almost unconscious. Direct laryngoscopy, which was easily performed without additional drugs, confirmed our suspicions of a bilateral abductor palsy. An endotracheal tube was passed, but colour and respiration were still not satisfactory. A short trial with a 5 per cent carbon dioxide-oxygen mixture did not improve the respiration, so the patient was connected to a Waters circuit and inflated

with oxygen through a soda lime canister. This produced dramatic improvement, and the patient regained consciousness sufficiently to sign her own consent, with evident insight, for tracheotomy. She was, however, now completely apnoeic. Inflation was continued on the way to theatre, and a little cyclopropane was added during the tracheotomy. A cut-down cuffed Magill tube was inserted into the trachea and this was again attached to the Waters bag and an oxygen cylinder. When inflated for two to three minutes the patient would awaken and breathe spontaneously; if left to herself she would gradually become unconscious again after a further two to three minutes and respiration would become periodic and finally cease.

This state of affairs continued throughout the afternoon and evening, in spite of giving 60 ml of 50 per cent sucrose in an attempt to reduce any possible cerebral oedema. I felt that there was little point in using hypothermia in this case, principally because during the periods of consciousness the patient showed no evidence of anoxic damage to the brain; power and tone were normal in all limbs, her expression was intelligent, she responded appropriately to questions and instructions, and tried hard to co-operate.

At midnight, I saw the patient with Dr. J. W. Dundee, who suggested that it might be interesting to give nikethamide in order to determine whether the respiratory centre was still capable of responding to a stimulus. Six ml of nikethamide were given intravenously and 4 ml intramuscularly, whereupon the patient began to breathe adequately on her own, and regained consciousness without the assistance of manual ventilation. This improvement lasted for about six to seven minutes, after which increasingly long respiratory pauses and some drowsiness reappeared. It seemed clear that as respiration failed the patient was becoming more and more sleepy, and as she became more sleepy she also became less and less capable of making the effort which seemed necessary for her to continue breathing. With this in mind I tried the effect of shaking the patient gently to arouse her attention, and simply telling her to keep on breathing. She responded instantly to this treatment, and respiration continued as long as she was prompted. Ten mg of amphetamine sulphate were given subcutaneously, and repeated with nikethamide 4 ml every four hours. A nurse was left by the bedside throughout the night with strict instructions to keep the patient awake and remind her to breathe.

By the following morning respiration was almost automatic, and subsequent improvement was rapid and complete. She has now had a submucous resection of one vocal cord, and her airway is satisfactory. I should like to thank Mr. F. Bauer for permission to publish this case.

J. PARKHOUSE
Walton Hospital, Liverpool

USE OF A MODIFIED BEAVER RESPIRATOR

Sir,—I was very interested in the paper by Dr. Jaques (*Brit. J. Anaesth.* (1957), **29**, 181) because the situation she describes not infrequently arises in our daily work.

The explanation given is captivating. However, it seems to me that a more simple interpretation and treatment should be thought of before hurrying a modified Beaver respirator into the theatre.

Trouble began after the patient had been positioned on the table and connected to a closed circuit, when controlled respiration by manual compression of the bag was found to be difficult, and this lasted until connection had been made with the Beaver respirator: "the improvement came within seconds."

When an endotracheal tube is kinked, when its bevel is lying against the wall of the trachea or carina, a little turning or pulling, as the result of reconnecting it, is often sufficient to remove the obstruction within seconds.

In my experience this mechanism sometimes plays a role in cases of respiratory obstruction in intubated patients. It is wise, therefore, not to rely blindly upon the patency of the tube, but to prove this by passing a wide-bore suction catheter through it.

If we exclude the endotracheal tube (and the other parts of the anaesthetic circuit) as the cause of this event, the description in the case history seems to point to bronchospasm.

It is not improbable that an injection of ephedrine, followed if necessary by aminophylline into the drip would have brought things under control.

This does not, however, detract from the value of the modified Beaver respirator with negative pressure in such a case.

J. D. P. WOLFF
Amsterdam, Holland

THE PHYSIOLOGICAL ACTION OF NEUROMUSCULAR AND GANGLIONIC BLOCKING AGENTS

Sir,—I was interested to read Professor J. H. Burn's most instructive paper on neuromuscular blocking agents. (*Brit. J. Anaesth.* (1957), **29**, 242) and was particularly struck by his advocacy of the use of ephedrine to potentiate the action of neostigmine in neutralizing the effects of d-tubocurarine and gallamine.

I have been teaching the use of ephedrine in this way for the past three years, but with the additional object of preventing the later development of the condition sometimes called " Prostigmine shock ", which is probably identical with the state that used to be known as " re-curarization ".

This use of ephedrine has two advantages; the neutralizing action of neostigmine is potentiated, while its depressant effect on the vital centres is counteracted. The muscular action can be clearly seen if the neostigmine is followed, after a lapse of two or three minutes, by a small intravenous injection of ephedrine (say $\frac{1}{8}$ to $\frac{1}{4}$ grain), the remainder of the $\frac{1}{2}$ grain (30 mg) being given intramuscularly or subcutaneously. It must be made clear that ephedrine should not be given intravenously in these circumstances until the neostigmine has begun to produce its effect because when administered experimentally together with atropine, ephedrine has increased the sinus rate to 200 per minute often with AV block (Sollman, 1950). E.c.g. monitoring has been done on a number of cases during the administration of this atropine-neostigmine-ephedrine sequence, and a few continuous tracings have been taken. A typical one shows a sinus rate of 70 per minute, rising to 132 two minutes after an intravenous injection of atropine 0.6 mg; neostigmine 1 mg was then given, and two minutes later the rate had fallen to 90. After ephedrine $\frac{1}{4}$ grain (15 mg) intravenously the rate settled at 84; there was no significant change in the e.c.g. complexes.

It is encouraging to find this use of ephedrine advocated by so eminent an authority as Professor Burn.

D. ZUCK
Chase Farm Hospital, Middlesex

REFERENCE

Sollman, T. (1950). *A Manual of Pharmacology*, 7th ed., p. 381.

DOSES OF CURARE: A PLEA FOR THEIR REDUCTION

Sir,—In my article on Doses of Curare (*Brit. J. Anaesth.* (1957), **29**, 228) I quoted Sadove, Wyant et al. as needing only 6–8 mg d-tubocurarine (dtc) for intubation of patients undergoing mitral valvulotomy. However, the drug they used was dimethyl tubocurarine which is 2–2½ times as potent; therefore their dose corresponds to about 12–20 mg dtc. As this amount is still about half the one used by Grigor for the same purpose the argument for reducing the dose of dtc remains unchanged.

LUISE WISLICKI
Jerusalem, Israel

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(5) The preparation is stable.

(6) The preparation does not attack rubber tubes.

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Literature will be sent on request.

DUNCAN FLOCKHART of Edinburgh

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